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EFFECT OF BILATERAL RESECTION OF THE SPLANCHNIC NERVES ON GASTRIC MOTILITY IN MAN

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During the past fifteen years numerous attempts have been made to correct certain abnormal physiologic states by the surgical interruption of various nervous pathways. Among these operative procedures, unilateral and bilateral resections of the splanchnic nerves have been frequently employed. In 1921 Jean [1] performed resection of the splanchnic nerves for the relief of pyloric spasm, hyperacidity and gastric hypersecretion. Daniélopolu [2] recommended the same procedure for the management of hypertension. For a few years resection of the left splanchnic nerves was considered adequate for the production of clinical relief in arterial hypertension. Craig and Brown [3] performed unilateral and bilateral resection of the major and minor splanchnic nerves for the relief of essential hypertension in young persons and concluded that it was a justifiable procedure in the early stages of the severe progressive form. The interruption of other nervous pathways [4] has been attempted

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1. Jean, G.: Les nerfs splanchniques au point de vue chirurgical, Arch. de. méd. et pharm. nav. **111**:292, 1921.

2. Daniélopolu, quoted by Craig and Brown.[3]

3. Craig, Winchell M., and Brown, George E.: Unilateral and Bilateral Resection of the Major and Minor Splanchnic Nerves: Its Effects in Cases of Essential Hypertension, Arch. Int. Med. **54**:577 (Oct.) 1934.

4. Page, Irvine H., and Heuer, George J.: A Surgical Treatment of Essential Hypertension, J. Clin. Investigation **14**:22 (Jan.) 1935; The Effect of Renal Denervation on the Level of Arterial Blood Pressure and Renal Function in Essential Hypertension, ibid. **14**:27 (Jan.) 1935.

for the control of this disease, with varying results. In 1927 Pieri [5] performed unilateral resection of the splanchnic nerves for intestinal atony, and recently de Takáts and his associates, on an experimental basis,[6] recommended bilateral resection of these nerves for the relief of juvenile diabetes.

In evaluating the effects of this surgical procedure, the primary interest of most investigators has been directed to subsequent manifestations of clinical improvement. These have been variable, owing, perhaps, to the extent and duration of the underlying disease. However, unilateral and bilateral resection of the splanchnic nerves have made available opportunities for investigating the specific functions of these nerves and their rôle in the body economy.

Many concepts regarding the physiology of the human splanchnic nerves have been derived from experimentation on animals. Some views, not entirely accurate, have persisted for many years without challenge. Thus, the investigations of Bayliss and Starling [7] in 1899 indicated that the splanchnic nerves exert a tonic inhibitory influence on intestinal movement. At no time did they obtain evidence that these nerves possess a motor function. Subsequent experimentation has altered this view.[8] More accurate information regarding the manifold function of the human splanchnic nerves will be available when direct observations are made on man. This is now possible owing to the frequency with which resection of the splanchnic nerves is being employed in the management of various diseases.

Recently an opportunity for studying objectively one function of the splanchnic nerves—namely, their influence on the human gastric motor mechanism—became possible when bilateral resection of the splanchnic nerves was accomplished for the control of severe diabetes.[6] A review of the literature has failed to reveal any reference to another study of this kind. The purpose of this paper is to report the results of our observations.

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5. Pieri, Gino: La resezione dei nervi splancnici, Ann. ital. di chir. **6**:678 (July) 1927; quoted by Craig and Brown.[3]

6. (*a*) de Takáts, Géza, and Cuthbert, F. P.: Surgical Attempts at Increasing Sugar Tolerance, Arch. Surg. **26**:750 (May) 1933. (*b*) de Takáts, Géza, and Fenn, G. K.: Bilateral Splanchnic Nerve Section in a Juvenile Diabetic, Ann. Int. Med. **7**:422 (Oct.) 1933. (*c*) de Takáts, Géza; Fenn, G. K., and Trump, Ruth A.: Splanchnic Nerve Section in Juvenile Diabetes, ibid. **7**:1201 (April) 1934.

7. Bayliss, W. M., and Starling, E. H.: The Movements and Innervation of the Small Intestine, J. Physiol. **24**:99, 1899.

8. Barry, D. T.: The Functions of the Great Splanchnic Nerves, J. Physiol. **75**:480, 1932.

PROCEDURE

The patient, a cooperative white man of 28, was trained to swallow a condom balloon attached to the end of a Rehfuss tube in place of the metal bulb. The tube was then connected to a bromoform manometer. In order that we might know accurately the location of the balloon in the stomach, a balloon coated with barium sulfate[9] was first swallowed, and its position was ascertained by means of the fluoroscope and by roentgenograms (fig. 1). The length of rubber tubing from this position to the incisor teeth was 54 cm. This distance was kept constant throughout

Fig. 1.—Roentgenogram demonstrating the balloon coated with barium sulfate in the stomach.

the observations. At the beginning of each experiment, the balloon was inflated to a pressure of 2 cc. of bromoform, and gastric motility was recorded on a slowly revolving kymograph (fig. 2). An automatic timer, recording every five seconds, was incorporated into the system. This made it possible to determine accurately the duration of and the interval between contractions. Observations were made in the morning, fourteen hours after the preceding meal, and were continued for a period of about five hours.

9. Carlson, A. J.: The Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1916.

TABLE 1.—*Analysis of Preoperative Control Experiments on Gastric Motility* *

Date of Experiment	Duration of Experiment	Number of Periods of Quiescence	Duration of Periods of Quiescence	Number of Periods of Activity	Duration of Periods of Activity	Contractions					Comment
						Type	Number	Duration	Interval Between	Amplitude	
9/13/34	5 hr. 30 m.	1	61 m.	1	70 m. 55 s.	Low grade	Inestimable	Inestimable	5 s.	Low grade	Fluctuations in gastric tonus
				1	155 m. 5 s.	II	205	Max. 1 m.	Max. 45 s.	Max. 3.5 cm.	Following this period of activity, the stomach went into a state of quiescence lasting 61 minutes
								Min. 5 s.	Min. 2 s.	Min. 1.2 cm.	
10/ 7/34	4 hr. 30 m.	1	10 m. 20 s.	1	41 m. 30 s.	Low grade	Inestimable	Inestimable	Inestimable	Low grade	Tonus changes resembling Traube-Herring waves
		1	30 m. 55 s.	1	88 m. 20 s.	II	86	Max. 45 s.	Max. 1 m. 35 s.	Max. 5.5 cm.	
		1	20 m.					Min. 18 s.	Min. 27 s.	Min. 0.7 cm.	
				1	81 m. 30 s.	II	45	Max. 27 s.	Max. 2 m. 50 s.	Max. 9 cm.	
								Min. 18 s.	Min. 27 s.	Min. 2 cm.	
10/10/34	5 hr.	1	29 m. 10 s.	1	42 m.	I	Inestimable	18 s. (av.)	Max. 27 s.	Low grade	
		1	29 m. 55 s.	..	.....	..	.....	.....	Min. 5 s.		
		1	39 m. 25 s.	1	74 m.	II	49	Max. 40 s.	Max. 1 m. 35 s.	Max. 7.5 cm.	
		1	23 m. 50 s.	..	.....	..	.....	Min. 18 s.	Min. 20 s.	Min. 1.5 cm.	
				1	30 m. 25 s.	I	Inestimable	Inestimable	Inestimable	Low grade	
				1	28 m. 20 s.	I	Inestimable	Inestimable	Inestimable	Low grade	
11/ 4/34	3 hr. 45 m.	1	20 m. 30 s.	1	61 m.	I	Inestimable	Inestimable	Inestimable	Low grade	Tonus changes resembling Traube-Herring waves
				1	82 m. 35 s.	I	Inestimable	Inestimable	Inestimable	Low grade	Fluctuations in gastric tonus
				1	57 m. 55 s.	II	76	Max. 54 s.	44 s. (av.)	Max. 15.5 cm.	
								Min. 18 s.		Min. 2 cm.	
11/ 6/34	3 hr. 30 m.	..	....	1	30 m. 55 s.	I	Inestimable	Inestimable	Inestimable	Low grade	
				1	27 m. 5 s.	II	35	Max. 18 s.	5 s. (av.)	Max. 15 cm.	
								Min. 5 s.		Min. 1 cm.	
				1	39 m.	I and II	Inestimable	Inestimable	Inestimable	Max. 3.5 cm.	
										Min. 0.8 cm.	
11/ 7/34	4 hr. 5 m.	1	39 m.	1	42 m.	I	Inestimable	Inestimable	Inestimable	Low grade	Low grade tonus changes
		1	18 m.	1	56 m.	I	Inestimable	Inestimable	Inestimable	Low grade	Low grade tonus changes
				1	60 m.	II	35	20 (av.)	Max. 2 m. 30 s.	Max. 2.2 cm.	
									Min. 40 s.	Min. 1.1 cm.	

11/ 8/34	5 hr. 45 m.	1	40 m.	1	68 m.	II	82	Max. 30 s. Min. 20 s.	Max. 1 m. 40 s. Min. 15 s.	Max. 4.1 cm. Min. 1.6 cm.	
		1	64 m.	1	20 m.	I	Inestimable	Inestimable	Inestimable	Low grade	Low grade tonus changes
				1	150 m.	II	140	Max. 30 s. Min. 20 s.	Max. 1 m. 30 s. Min. 5 s.	Max. 4.1 cm. Min. 1 cm.	This was followed by a period of quiescence during which time the experiment was discontinued
11/ 9/34	2 hr. 45 m.	1	33 m. 10 s.	1	107 m.	I and II	Inestimable	Inestimable	Inestimable	Low grade	6 m. 15 s. before end of experiment contractions became violent
11/10/34	3 hr. 45 m.	1	6 m. 10 s.	1	37 m. 40 s.	I	Inestimable	Inestimable	Inestimable	Low grade	
				1	97 m. 20 s.	II	93	18 s. (av.)	Max. 6 m. Min. 9 s.	Max. 13.1 cm. Min. 1.5 cm.	
		1	48 m. 15 s.	1	83 m.	I	Inestimable	Inestimable	Inestimable	Low grade	One violent contraction 8 m. before end of experiment; amplitude 8.7 cm.; otherwise low grade activity
11/12/34	5 hr. 5 m.	..	.....	1	65 m.	I	Inestimable	Inestimable	Inestimable	Low grade	
		1	13 m.	1	184 m.	I and II	Inestimable	Max. 50 s.	Max. 40 s.	Max. 1.7 cm.	Because of the variability of the type of contractions the number was not counted
							Remarks	Min. 20 s.	Min. 20 s.	Min. 0.5 cm.	
11/13/34	5 hr. 30 m.	1	83 m.	..	Remarks	I	Inestimable	Inestimable	Inestimable	Low grade	The period of quiescence merged with the period of low grade activity; these periods could not be demarcated
				1	127 m.	II	99	Max. 1 m. 10 s. Min. 20 s.	Max. 3 m. 20 s. Min. 20 s.	Max. 4.1 cm. Min. 1 cm.	
		1	36 m. 4 s.	1	61 m.	II	87	Max. 20 s. Min. 10 s.	Max. 3 m. Min. 30 s.	Max. 8.6 cm. Min. 0.7 cm.	
		1	17 m. 25 s.	..	.....	..	.....	.....	.....	.....	Experiment terminated at this time
11/15/34	4 hr. 50 m.	The stomach was in a constant state of low grade activity; no concrete contractions noted; some fluctuations in tonus									
11/16/34	5 hr.	Constant state of low grade motility with slight changes in tonus; no definite contractions									
11/21/34	2 hr. 5 m.	Constant state of low grade motility with slight changes in tonus; no definite contractions									
11/22/34	3 hr. 5 m.	..	.....	1	60 m. 45 s.	I	Inestimable	Inestimable	Inestimable	Low grade	
		1	6 m. 45 s.	1	165 m.	I and II	Remarks	Max. 1 m. Min. 10 s.	Max. 2 m. Min. 10 s.	Max. 5 cm. Min. 0.7 cm.	The number of contractions could not be counted, many contractions merged with deep respirations which obscured the actual gastric contraction

* In this table and in tables 2 and 3, m. indicates minutes; s., seconds; Min., minimum, and Max., maximum.

TABLE 2.—*Analysis of Experiments on Gastric Motility After Resection of the Left Splanchnic Nerves*

Date of Experiment	Duration of Experiment	Number of Periods of Quiescence	Duration of Periods of Quiescence	Number of Periods of Activity	Duration of Periods of Activity	Contractions					Comment
						Type	Number	Duration	Interval Between	Amplitude	
12/ 6/34	5 hr. 15 m.	1	9 m.	1	15 m. 5 s.	II	13	Max. 1 m. 10 s. Min. 40 s.	Max. 1 m. Min. 30 s.	Max. 3.2 cm. Min. 0.7 cm.	
		1	14 m. 10 s.	1	23 m. 20 s.	II	24	Max. 50 s. Min. 5 s.	Max. 1 m. Min. 5 s.	Max. 3.5 cm. Min. 1 cm.	
		1	21 m. 15 s.	1	30 m. 45 s.	II	22	Max. 55 s. Min. 20 s.	Max. 1 m. 25 s. Min. 30 s.	Max. 4.1 cm. Min. 1.1 cm.	During each period of quiescence there was evidence of changes of tonus
		1	21 m. 30 s.	1	28 m. 30 s.	II	18	Max. 40 s. Min. 5 s.	Max. 2 m. 35 s. Min. 5 s.	Max. 3.8 cm. Min. 1.1 cm.	
		1	22 m. 10 s.	1	31 m. 25 s.	II	19	Max. 50 s. Min. 30 s.	Max. 3 m. Min. 45 s.	Max. 3.5 cm. Min. 0.8 cm.	
		1	93 m. 45 s.	..	.....	..	.....	.....	.....	.....	Experiment terminated
12/ 7/34	4 hr. 45 m.	1	19 m. 20 s.	1	66 m. 30 s.	I	Inestimable	Inestimable	Inestimable	Max. 2.3 cm. Min. 0.5 cm.	Almost continuous gastric activity with a few severe contractions
		1	9 m. 25 s.	1	45 m. 25 s.	I and II	18	Max. 35 s. Min. 5 s.	Max. 3 m. 25 s. Min. 1 m. 10 s.	Max. 4 cm. Min. 1.2 cm.	
		1	57 m. 50 s.	1	75 m. 55 s.	I and II	16	Max. 45 s. Min. 15 s.	Max. 1 m. 25 s. Min. 55 s.	Max. 3.7 cm. Min. 1.5 cm.	
12/ 9/34	4 hr.	1	17 m. 10 s.	1	75 m. 10 s.	I and II	Inestimable	Max. 50 s. Min. 20 s.	Max. 3 m. Min. 20 s.	Max. 7.3 cm. Min. 1 cm.	
		1	97 m. 45 s.	1	35 m. 25 s.	1	Inestimable	Inestimable	Inestimable	Low grade	16 m. after onset of experiment, 40 units of insulin was administered without any appreciable change in motility
12/10/34	6 hr. 10 m.	1	34 m.	1	73 m.	I and II	45	Max. 1 m. Min. 20 s.	Max. 1 m. 25 s. Min. 30 s.	Max. 4.5 cm. Min. 1.4 cm.	
		1	19 m. 10 s.	1	14 m. 45 s.	II	6	Max. 55 s. Min. 30 s.	Max. 2 m. Min. 1 m.	Max. 1.4 cm. Min. 0.7 cm.	
		1	43 m. 25 s.	1	55 m.	I and II	32	Max. 1 m. Min. 15 s.	Max. 2 m. Min. 1 m. 20 s.	Max. 2.5 cm. Min. 0.5 cm.	
		1	11 m. 55 s.	1	52 m.	I and II	24	Max. 50 s. Min. 20 s.	Max. 1 m. 30 s. Min. 35 s.	Max. 4.4 cm. Min. 0.6 cm.	

12/12/34	5 hr.	..	.....	1	22 m. 25 s.	II	22	Max. 55 s. Min. 5 s.	Max. 25 s. Min. 5 s.	Max. 4.3 cm. Min. 1 cm.	
		1	34 m. 25 s.	1	242 m.	II	163	Max. 50 s. Min. 15 s.	Max. 2 m. Min. 25 s.	Max. 5.4 cm. Min. 1.1 cm.	
12/13/34	5 hr.	..	.....	1	116 m. 10 s.	I and II	45	Max. 1 m. Min. 25 s.	Max. 6 m. 25 s. Min. 1 m.	Max. 3.9 cm. Min. 0.6 cm.	
		1	30 m. 15 s.	1	45 m.	II	21	Max. 1 m. Min. 5 s.	Max. 3 m. Min. 1 m. 30 s.	Max. 4.2 cm. Min. 2 cm.	
		1	38 m. 40 s.	1	60 m. 15 s.	II	28	Max. 1 m. Min. 25 s	Max. 4 m. 25 s. Min. 1 m. 25 s.	Max. 3.8 cm. Min. 1.3 cm.	Experiment terminated
12/14/34	5 hr. 5 m.	..	.....	1	196 m.	II	92	Max. 1 m. 15 s. Min. 15 s.	Max. 5 m. Min. 1 m.	Max. 4.8 cm. Min. 1 cm.	
		1	107 m.	..	.....	..	.....	.....	.....	.....	
1/ 4/35	3 hr. 25 m.	..	.....	1	175 m. 35 s.	II	143	Max. 50 s. Min. 20 s.	Max. 1 m. 35 s. Min. 20 s.	Max. 4.7 cm. Min. 0.8 cm.	82 m. after start of experiment patient was given injection of atropine, 1/150 grain; no alteration in gastric motility
		1	11 m. 10 s.	1	18 m. 10 s.	I and II	Inestimable	Inestimable	Inestimable	Low grade	
1/ 5/35	4 hr.	..	.....	1	240 m.	II	228	Max. 1 m. Min. 10 s.	Max, 2 m. 20 s. Min. 30 s.	Max. 4.5 cm. Min. 0.6 cm.	55 m. after onset of experiment blood sugar drawn; period of quiescence followed
1/16/35	4 hr. 35 m.	1	22 m. 40 s.	1	172 m.	I and II	170	Max. 1 m. 10 s. Min. 25 s.	Max. 2 m. Min. 5 s.	Max. 9 cm. Min. 1 cm.	
		1	72 m. 20 s.	..	.....	..	.....	.....	.....	.....	Experiment terminated at this time
1/23/35	4 hr. 4 m.	1	10 m. 25 s.	1	227 m.	II and III	95	Max. 1 m. 35 s. Min. 15 s.	Max. 2 m. 25 s. Min. 40 s.	Max. 5 cm. Min. 1.4 cm.	Severe motility lasting 105 m. 35 s., type III contractions observed; type II contraction for 120 m., 40 s.; experiment ended during, period of quiescence
1/26/35	5 hr.	..	.....	1	67 m.	III	Inestimable	Inestimable	Inestimable	Max. 7.5 cm. Min. 1.5 cm.	Severe motility; period terminated in gastric tetany
		1	21 m.	1	215 m.	II and III	169	Max. 40 s. Min. 10 s.	Max. 2 m. 15 s. Min. 15 s.	1 cm.	Severe motility at beginning of period lasting 60 m.; type II contractions for 155 m.
1/30/35	5 hr.	..	.....	1	44 m.	III	Inestimable	Inestimable	Inestimable	Max. 3 cm. Min. 0.5 cm.	Severe motility ending in gastric tetany
		1	8 m. 15 s.	1	75 m. 10 s.	III	Inestimable	Inestimable	Inestimable	Max. 4 cm. Min. 0.5 cm.	Severe motility ending in gastric tetany
		1	15 m. 40 s.	1	156 m.	II	128	Max. 1 m. Min. 30 s.	Max. 2 m. 15 s. Min. 20 s.	Max. 6 cm. Min. 1.5 cm.	

TABLE 2.—*Analysis of Experiments on Gastric Motility After Resection of the Left Splanchnic Nerves—Continued*

Date of Experiment	Duration of Experiment	Number of Periods of Quiescence	Duration of Periods of Quiescence	Number of Periods of Activity	Duration of Periods of Activity	Contractions					Comment
						Type	Number	Duration	Interval Between	Amplitude	
2/ 5/35	5 hr.	..	.....	1	300 m.	II and III	Inestimable	Inestimable	Inestimable	Max. 3.5 cm. Min. 0.5 cm.	Constant, moderately severe motility; no periods of quiescence; gastric tetany noted; motility varied between type II and type III
2/ 8/35	4 hr.	..	.....	1	58 m.	I and III	Inestimable	Inestimable	Inestimable	Max. 2.5 cm. Min. 0.5 cm.	Period terminated in gastric tetany
		1	9 m.	1	180 m.	II	200	Max. 1 m. Min. 15 s.	Max. 1 m. 10 s. Min. 10 s.	Max. 4 cm. Min. 1 cm.	
2/11/35	5 hr. 7 m.	1	12 m. 40 s.	1	40 m. 35 s.	III	Inestimable	Inestimable	Inestimable	Max. 4 cm. Min. 0.7 cm.	Constant severe motility with periods of gastric tetany
		1	9 m.	1	301 m.	II	311	Max. 1 m. Min. 20 s.	Max. 3 m. 15 s. Min. 20 s.	Max. 5.5 cm. Min. 1.5 cm.	Experiment terminated during period of activity
2/13/35	5 hr.	..	.....	1	46 m.	III	Inestimable	Inestimable	Inestimable	Max. 3.5 cm. Min. 1 cm.	Gastric tetany observed at end of this period
		1	11 m. 30 s.	1	172 m. 20 s.	II	169	Max. 1 m. 45 s. Min. 10 s.	Max. 4 m. Min. 5 s.	Max. 14 cm. Min. 1.5 cm.	Period of activity followed by quiescence during which an occasional contraction was observed
2/15/35	5 hr. 22 m	..	.....	1	322 m.	II and III	Inestimable	Inestimable	Inestimable	2 cm.	Periods of incomplete tetany observed; this followed by period of type II contractions lasting 201 m. 25 s.
2/19/35	6 hr. 5 m.	..	.....	1	48 m. 15 s.	II and III	Inestimable	Inestimable	Inestimable	.....	Period of tetany lasting 16 m.
		1	15 m. 45 s.	1	295 m.	II and III	291	Max. 45 s. Min. 20 s.	Max. 1 m. Min. 15 s.	Max. 5 cm. Min. 1.5 cm.	Duration of type II contractions 220 m. 35 s.; one period of tetany lasting 8 m. 20 s.
2/20/35	5 hr. 5 m.	..	.....	1	305 m.	III	Inestimable	20 s.	30 s.	2.5 cm.	Contractions were uniform; stomach showed continuous motility
2/27/35	6 hr. 45 m.	1	10 m. 45 s.	1	48 m. 40 s.	III	Inestimable	Inestimable	Inestimable	Max. 3 cm. Min. 1.5 cm.	Periods of tetany lasting 10 m.
				1	344 m.	II and III	285	Max. 1 m. Min. 25 s.	Max. 1 m. Min. 15 s.	Max. 5 cm. Min. 2 cm.	Duration of type III contraction, 2 hr. 9 m. Duration of type II contraction, 3 hr. 35 m.

Fifteen preoperative control observations were made (table 1) prior to bilateral resection of the splanchnic nerves. This was done in two stages. On Nov. 28, 1934, resection of the left splanchnic nerves was accomplished. Studies of gastric motility were resumed eight days after the operation. Twenty-one postoperative observations (table 2) were made under the same conditions as obtained during the control period. Resection of the right splanchnic nerves was then performed on March 4, 1935, the same technic being utilized as in the previous operation. Studies of gastric motility were again undertaken about a week postoperatively, and twenty-five subsequent observations (table 3) were made.

Stage I: Resection of the Left Splanchnic Nerves, Nov. 28, 1934.—With the patient under gas anesthesia, a curved paravertebral incision was made over the inner ends of the ninth, tenth and eleventh ribs. The longitudinal muscles were carefully separated from their costal attachments and were retracted laterally. The inner ends of the ninth, tenth and eleventh ribs were freed, disarticulated and resected. To increase the exposure, parts of the transverse processes were

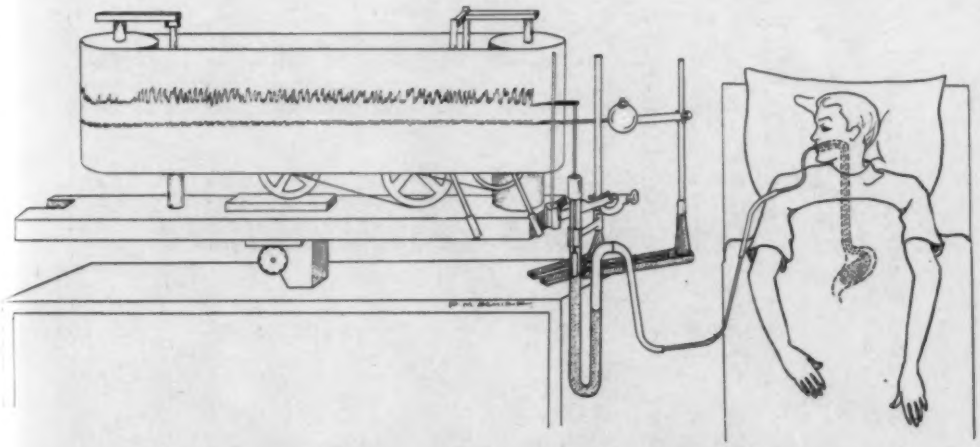

Fig. 2.—Diagram of apparatus used to record gastric motility.

removed with a rongeur. The thin pleura was retracted laterad. The posterior mediastinum was then entered. The splanchnic nerves were identified. A number of branches extending through the diaphragm were found. These arose from the ganglionated cord. In all there were two large and five small branches. These were dissected, and 3 to 5 cm. segments were resected. All connections with the ganglionated cord were severed. The region was thoroughly explored for accessory splanchnic nerves. None were found. The wound was closed in layers. Throughout the operation no complication was encountered. Immediately after the resection of the left splanchnic nerves there was no precipitous drop in the blood pressure. The postoperative convalescence was uncomplicated. Shortly after the operation the blood pressure gradually fell to a low level, but at no time were untoward symptoms apparent.

Stage II: Resection of the Right Splanchnic Nerves, March 4, 1935.—The technic and details of this stage were essentially the same as those in the first stage. No complications occurred, and recovery was rapid. Postoperatively, the drop in blood pressure was not so marked as that which occurred after the first

TABLE 3.—*Analysis of Experiments on Gastric Motility After Resection of the Right Splanchnic Nerves*

Date of Experiment	Duration of Experiment	Number of Periods of Quiescence	Duration of Periods of Quiescence	Number of Periods of Activity	Duration of Periods of Activity	Contractions					Comment
						Type	Number	Duration	Interval Between	Amplitude	
3/11/35	5 hr.	..	.....	1	15 m. 30 s.	II and III	Inestimable	Inestimable	Inestimable	Inestimable	Contractions occurred rapidly
		1	16 m. 30 s.	1	266 m.	II	201	Max. 1 m. Min. 30 s.	Max. 3 m. 20 s. Min. 40 s.	Max. 8.5 cm. Min. 2 cm.	
3/13/35	5 hr. 35 m.	..	.....	1	27 m.	I and II	Inestimable	Inestimable	Inestimable	Low grade	
		1	42 m.	1	266 m.	II	175	Max. 1 m. Min. 20 s.	Max. 2 m. 40 s. Min. 1 m.	Max. 5 cm. Min. 2 cm.	Terminated in activity
3/15/35	5 hr. 30 m.	1	13 m. 35 s.	1	27 m.	II	26	Max. 1 m. Min. 20 s.	Max. 1 m. Min. 15 s.	Max. 3.5 cm. Min. 2 cm.	
		1	21 m. 30 s.	1	267 m.	II	176	Max. 50 s. Min. 20 s.	Max. 2 m. Min. 30 s.	Max. 5.5 cm. Min. 1.2 cm.	
3/19/35	5 hr.	..	.....	1	300 m.	II	239	Max. 2 m. Min. 25 s.	Max. 3 m. 10 s. Min. 30 s.	Max. 5.5 cm. Min. 2 cm.	No quiescent periods
3/22/35	5 hr. 15 m.	..	.....	1	5 m.	II	5	Max. 25 s. Min. 15 s.	Max. 1 m. Min. 10 s.	Max. 6 cm. Min. 3.5 cm.	Short periods of severe motility interrupted by short periods of quiescence
		1	8 m. 45 s.	1	25 m.	II	29	Max. 1 m. 5 s. Min. 10 s.	Max. 1 m. 10 s. Min. 5 s.	Max. 9.5 cm. Min. 3 cm.	
		1	12 m. 10 s.	1	104 m. 25 s.	II	65	Max. 1 m. 15 s. Min. 20 s.	Max. 6 m. 20 s. Min. 20 s.	Max. 11 cm. Min. 4.5 cm.	
		1	15 m. 45 s.	1	19 m. 15 s.	II	16	Max. 55 s. Min. 30 s.	Max. 1 m. 5 s. Min. 30 s.	Max. 7.5 cm. Min. 3.5 cm.	
		1	9 m. 25 s.	1	25 m. 45 s.	II	22	Max. 45 s. Min. 25 s.	Max. 1 m. Min. 20 s.	Max. 7 cm. Min. 4 cm.	
		1	7 m. 20 s.	1	80 m. 55 s.	II	75	Max. 2 m. Min. 25 s.	Max. 1 m. 55 s. Min. 30 s.	Max. 6.5 cm. Min. 3 cm.	
3/24/35	4 hr. 30 m.	Continuous relatively low grade motility; type I and type II contractions									
3/27/35	5 hr.	.	.....	1	300 m.	I and II	Inestimable	Max. 1 m. Min. 10 s.	Max. 50 s. Min. 10 s.	Max. 3 cm. Min. 2 cm.	Type I and II could not be clearly differentiated

3/29/35	5 hr.	..	.....	1	300 m.	I and II	Inestimable	Max. 2 m. Min. 25 s.	Max. 1 m. Min. 20 s.	Max. 4 cm. Min. 2 cm.	
3/31/35	4 hr. 15 m.	..	.....	1	47 m.	II and III	Inestimable	Inestimable	Inestimable	Inestimable	Period ended in gastric tetany
		1	20 m.	1	188 m.	I and II	Inestimable	Max. 1 m. 40 s. Min. 30 s.	Max.3 m. Min. 20 s.	Max. 4. cm. Min. 2 cm.	
4/ 1/35	5 hr.	..	.....	1	23 m.	II and III	Inestimable	Inestimable	Inestimable	Inestimable	Period ended in gastric tetany
		1	14 m.	1	263 m.	II	273	Max. 1 m. Min. 30 s.	Max. 1 m. 30 s. Min. 35 s.	Max. 5.5 cm. Min. 1.5 cm.	
4/ 2/35	5 hr.	..	.....	1	61 m.	II and III	52	Max. 45 s. Min. 10 s.	Max. 3 m. Min. 20 s.	Max. 9 cm. Min. 2 cm.	
		1	50 m.	1	106 m.	II	67	Max. 50 s. Min. 15 s.	Max. 2 m. 15 s. Min. 50 s.	Max. 9 cm. Min. 2 cm.	
		1	35 m.	1	52 m.	II	33	Max. 50 s. Min. 15 s.	Max. 3 m. Min. 45 s.	Max. 6 cm. Min. 2 cm.	Terminated in activity
4/ 3/35	5 hr.	..	.....	1	88 m.	II and III	Inestimable	Max. 55 s. Min. 10 s.	Max. 55 s. Min. 20 s.	Max. 5.5 cm. Min. 1.5 cm.	
		1	69 m.	1	143 m.	I and II	112	Max. 1 m. Min. 25 s.	Max. 1 m. 20 s. Min. 25 s.	Max. 4.5 cm. Min. 1.5 cm.	
4/ 4/35	5 hr.	..	.....	1	300 m.	I and II	272	Max. 1 m. 10 s. Min. 30 s.	Max. 50 s. Min. 20 s.	Max. 5 cm. Min. 2 cm.	Type I, 106 m. Type II, 194 m.
4/ 5/35	5 hr. 20 m.	Continuous motility; type I and II contractions									
4/6/35	5 hr. 10 m.	..	.....	1	46 m.	II	47	Max. 50 s. Min. 25 s.	Max. 40 s. Min. 20 s.	Max. 4.5 cm. Min. 2.5 cm.	Period terminated in gastric tetany
		1	79 m.	1	185 m.	II	130	Max. 1 m. 30 s. Min. 20 s.	Max. 1 m. 50 s. Min. 40 s.	Max. 4.5 cm. Min. 2 cm.	
4/15/35	5 hr. 15 m.	..	.....	1	58 m.	I, III and III	Inestimable	Inestimable	Inestimable	Max. 3.5 cm. Min. 1.5 cm.	Period ended in gastric tetany
		1	7 m.	1	202 m.	I and II	256	Max. 1 m. 15 s. Min. 5 s.	Max. 4 m. Min. 5 s.	Max. 12 cm. Min. 2 cm.	
4/16/35	5 hr.	..	.....	1	160 m.	I and II	Inestimable	Inestimable	Inestimable	Max. 3 cm. Min. 1.5 cm.	
				1	140 m.	II	200	Max. 50 s. Min. 20 s.	Max. 30 s. Min. 5 s.	Max. 4.5 cm. Min. 2.5 cm.	
4/18/35	3 hr. 30 m.	..	.....	1	210 m.	II	212	Max. 45 s. Min. 5 s.	Max. 30 s. Min. 5 s.	Max. 4.5 cm. Min. 2 cm.	

TABLE 3.—*Analysis of Experiments on Gastric Motility After Resection of the Right Splanchnic Nerves—Continued*

Date of Experiment	Duration of Experiment	Number of Periods of Quiescence	Duration of Periods of Quiescence	Number of Periods of Activity	Duration of Periods of Activity	Contractions					Comment
						Type	Number	Duration	Interval Between	Amplitude	
4/19/35	4 hr. 45 m.	1	22 m.	1	256 m.	II	262	Max. 1 m. Min. 35 s.	Max. 1 m. 35 s. Min. 5 s.	Max. 6 cm. Min. 3 cm.	
4/21/35	5 hr. 40 m.	..	.....	1	94 m.	II	92	Max. 50 s. Min. 20 s.	Max. 40 s. Min. 20 s.	Max. 9 cm. Min. 2 cm.	
		1	47 m.	1	199 m.	II	163	Max. 1 m. Min. 10 s.	Max. 3 m. Min. 5 s.	Max. 10 cm. Min. 3 cm.	Intense motility throughout observation period
4/23/35	5 hr.	..	.....	1	67 m.	II and III	Inestimable	Inestimable	Inestimable	Max. 4 cm. Min. 2 cm.	This period ended in gastric tetany
		1	12 m.	1	221 m.	II	265	Max. 1 m. Min. 20 s.	Max. 2 m. 25 s. Min. 20 s.	Max. 4 cm. Min. 1.5 cm.	
4/24/35	5 hr. 20 m.	..	.....	1	111 m.	II	109	Max. 40 s. Min. 10 s.	Max. 1 m. 35 s. Min. 10 s.	Max. 12.5 cm. Min. 2 cm.	Intense motility
				1	59 m.	I	Inestimable	Inestimable	Inestimable	2 cm.	
				1	48 m.	II	63	Max. 1 m. 10 s. Min. 15 s.	Max. 1 m. 30 s. Min. 20 s.	Max. 6.5 cm. Min. 2 cm.	
				1	102 m.	I and II	Inestimable	Inestimable	Inestimable	Max. 3.5 cm. Min. 1.5 cm.	Continuous motility throughout observation period
4/26/35	5 hr.	..	.....	1	79 m.	I, II and III	Inestimable	Inestimable	Inestimable	Max. 3.5 cm. Min. 1 cm.	Period ended in gastric tetany; terminal period of type II motility
		1	9 m.	1	212 m.	I and II	97	Max. 50 s. Min. 40 s.	Max. 1 m. 20 s. Min. 10 s.	Max. 4.5 cm. Min. 2 cm.	
4/28/35	5 hr. 20 m.	..	.....	1	320 m.	II	387	Max. 50 s. Min. 5 s.	Max. 1 m. Min. 10 s.	Max. 4 cm. Min. 2 cm.	Continuous type II motility throughout observation period
4/29/35	5 hr.	..	.....	1	69 m.	I, II and III	Inestimable	Inestimable	Inestimable	Max. 5 cm. Min. 1.5 cm.	Period ended in gastric tetany
		1	32 m.	1	229 m.	II	198	Max. 1 m. Min. 30 s.	Max. 1 m. 40 s. Min. 25 s.	Max. 6 cm. Min. 3 cm.	

stage. There has been a gradual decrease in the patient's requirement of insulin. At present the condition is controlled with 30 units daily, in contrast to 100 units, which he required prior to surgical intervention.

RESULTS

The effects of bilateral resection of the splanchnic nerves on gastric motility were evaluated according to the following criteria: (1) duration of the experiment, (2) number of periods of quiescence, (3) duration of quiescence, (4) number of periods of activity, (5) duration of activity, (6) number of contractions during a period of activity, (7) duration of the contractions, (8) interval between contractions, (9) amplitude of contractions and (10) type of contractions.

The data accumulated during the control period are presented in table 1.

Fig. 3.—Kymographic tracing made on Oct. 7, 1934, showing relative gastric quiescence at the beginning of a period of observation. Respiratory movements or "gastric respirations" can be noted.

The normal empty living stomach is rarely, if ever, in a state of absolute quiescence. Experimentation[9] reveals rhythmic periods of motility alternating with periods of relative quiescence. During these there may be an absence of actual contractility, but a certain degree of gastric tonus is always present. Kymographic records, obtained by the balloon method during periods of relative quiescence, frequently reveal the influence of diaphragmatic excursions. These have been termed "gastric respirations" (fig. 3). With the bromoform manometer it is possible to record even the pulsations of the intra-abdominal vessels, superimposed on the fluctuations in gastric tonus.

In our experiments, periods of relative quiescence often occurred at the beginning. This may have been due to reflex motor inhibition of the stomach, subsequent to esophageal and gastric stimulation.[10] In

10. Carlson, A. J.: Gastric Hunger Contractions Inhibited Reflexly from the Mouth, Am. J. Physiol. **31**:212, 1913; Influence of Stimulation of the Gastric Mucosa on Gastric Hunger Contractions, ibid. **32**:245 and 389, 1913.

certain instances quiescence, appearing between periods of activity, exhibited an abrupt onset and an abrupt cessation. "Gastric respirations" frequently were associated with low grade fluctuations in tonus (fig. 4), followed by feeble contractions which became increasingly severe, making it difficult to differentiate between the cessation of quiescence and the onset of activity.

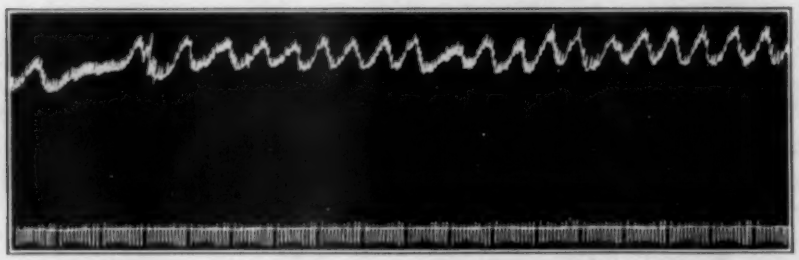

Fig. 4.—Tracing made on Nov. 16, 1934, showing feeble changes of tonus.

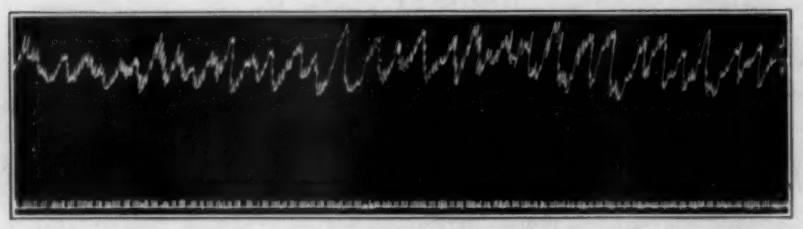

Fig. 5.—Type I contractions.

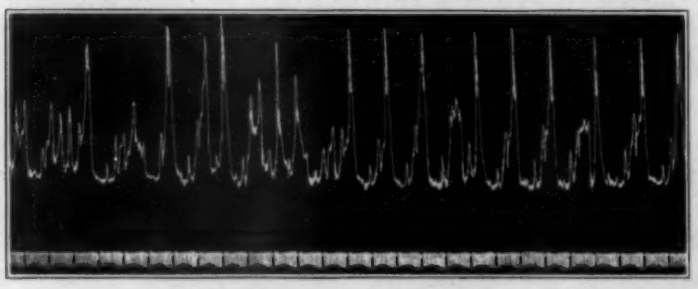

Fig. 6.—Type II contractions.

Gastric motility was analyzed according to Carlson's criteria.[9] Three types of contraction were recognized, depending on the degree of gastric tonus. Type I denotes a state of low grade tonus (fig. 5). Actual contractions are feeble, and the amplitude is low. This type of motility was commonly observed during the control period.

Type II contractions are associated with a relatively strong gastric tonus. These contractions occur in rapid succession without any marked intervening pause (fig. 6). Contractions of this type were observed

frequently. During periods of type II contractions, the number of, the duration of, the interval between, and the amplitude of, contractions were determined.

Contractions designated as type III occur when the stomach is in a state of tetany (fig. 7). This is characterized by periods of strong and relatively persistent tonus, on which are superimposed a series of rapid contractions. Type III was not observed during the control period. The various types of contractions, as observed, are presented in tables 1, 2 and 3.

The data accumulated subsequent to resection of the left splanchnic nerves are presented in table 2. The first four observations were more or less uniform, in that each exhibited short periods of intense motility

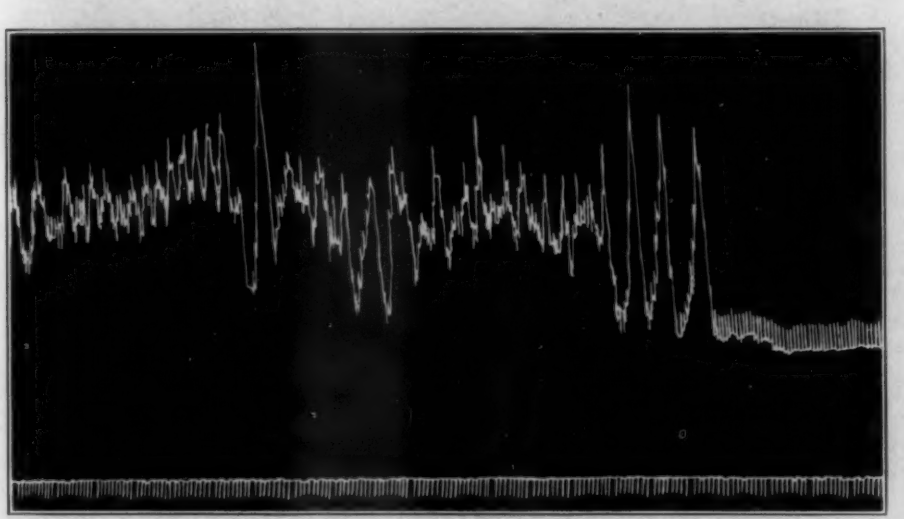

Fig. 7.—Type III contractions, or gastric tetany.

interrupted by short periods of quiescence (fig. 8). In the first of these observations the periods of activity were extremely short. The details are tabulated. In the three subsequent observations there was a definite increase in the duration of activity. Finally, in the seventeen subsequent experiments the outstanding feature was the persistent intense gastric motility (fig. 9).

Gastric motility was frequently observed at the beginning of the experiment. This persisted for approximately an hour and terminated in a very short period of quiescence, the duration of which was approximately ten to twelve minutes. Following quiescence, motility was resumed and usually continued throughout the period of observation. Often the motility ended abruptly in gastric tetany, which lasted approximately ten minutes. In the majority of instances the contractions were of type II, with no great variation in the duration of and the interval

between contractions. The number of contractions during a period of observation was increased. The reason for this was the prolonged duration of activity. There was a slight but definite increase in the amplitude of contractions. Type III contractions were common. The rapidity

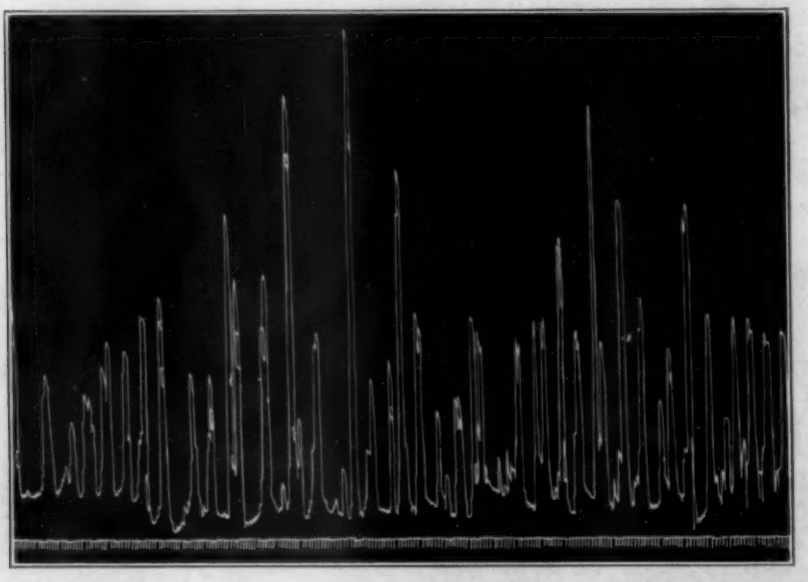

Fig. 8.—Tracing made on Feb. 13, 1935, showing intense gastric motility after resection of the left splanchnic nerves. The maximal amplitude of contractions was 14 cm.

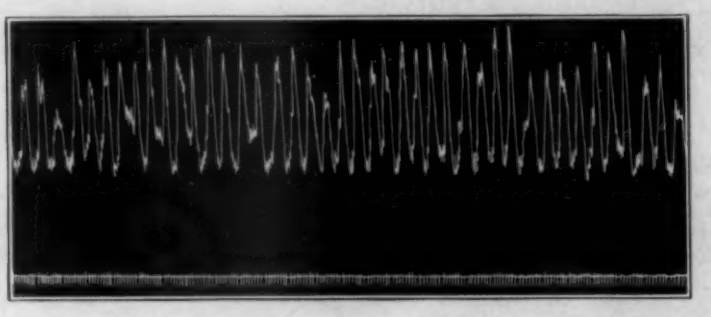

Fig. 9.—Tracing made on Feb. 27, 1935, showing persistent gastric motility after resection of the left splanchnic nerves. The duration of the period of activity was three hundred and forty-four minutes.

with which these contractions appeared made it impossible to evaluate accurately the number of, the duration of, and the interval between, contractions. Occasionally there was a blending of type II and type III, making it difficult to differentiate between the two.

The results subsequent to resection of the right splanchnic nerves were similar to those following the first stage (table 3). Twenty-five observations were made. Again the outstanding feature was the persistence of intense gastric motility (fig. 10). During some observations

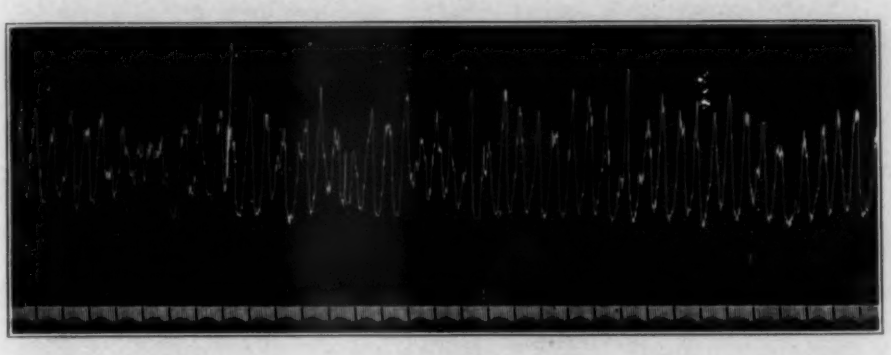

Fig. 10.—Tracing made on April 16, 1935, showing persistent gastric motility after resection of the right splanchnic nerves. The total duration of activity was three hundred minutes.

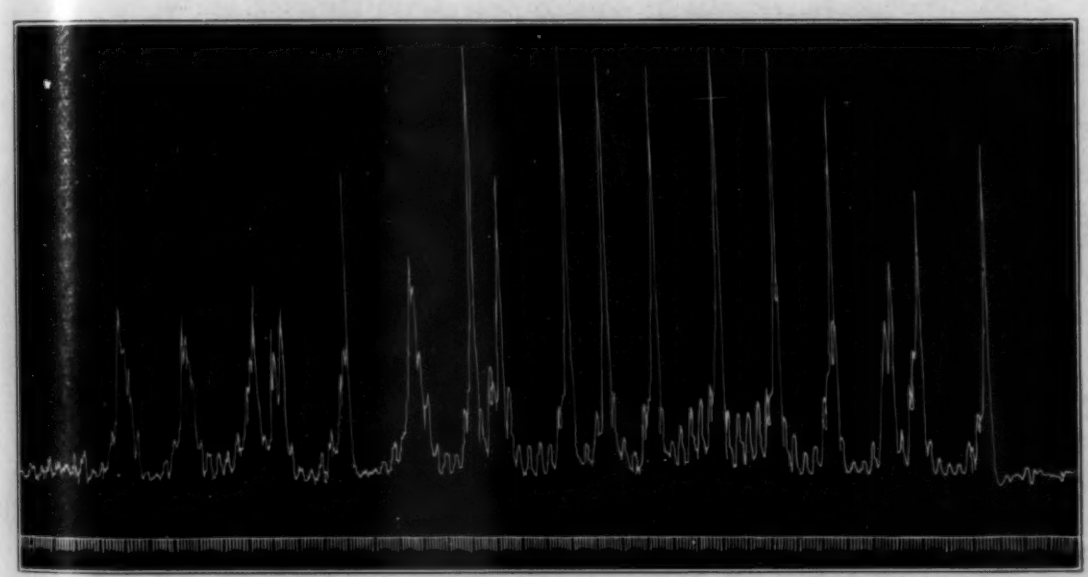

Fig. 11.—Tracing made on March 22, 1935, showing intense gastric motility after resection of the right splanchnic nerves. The maximal amplitude of contractions was 11 cm.

the contractions were even of sufficient magnitude to rupture the balloon and to force the bromoform almost from the manometer (fig. 11). Following them, there was a transitory decrease in gastric tonus, followed by contractions of great amplitude comparable to those just

described. In some experiments there was complete abolition of relative quiescence, the entire period of observation being one of intense gastric motility. Many experiments were similar to those following the resection of the left splanchnic nerves in that there was an initial short period of activity terminating in tetany. This was followed by a very short period of quiescence, after which the motility was continuous throughout the period of observation. No change of any magnitude was observed in the type of, the duration of, the interval between, or the amplitude of, contractions when they were compared with the results following resection of the left splanchnic nerves.

COMMENT

Abdominal and extra-abdominal surgery are frequently complicated by morbid physiologic processes which if uncorrected may proceed to a fatal termination.[11] Acute dilatation of the stomach and paralytic ileus still present pressing problems in their etiology and management.[12] The investigations of Brunemeier and Carlson[13] and Dragstedt[12] indicate that surgical intervention on the gastro-intestinal tract is associated with interference with efferent and afferent nervous pathways. These play an important rôle in the development of complications.

The work reported in this paper was undertaken to establish certain basic facts, on which can be constructed further investigation. This may yield information regarding the rôle of the mechanism of the gastro-intestinal motor nerves in the production and management of these perverted physiologic conditions.

The effects of bilateral resection of the splanchnic nerves on the gastric motility of dogs indicated an increase in gastric tonus and an augmentation of the contractions. Motility frequently was continuous throughout a period of observation of from two to four hours.[9] The results of our experiments on our patient confirm these findings. Tables 1, 2 and 3 illustrate that after bilateral resection of the splanchnic nerves there is a definite augmentation of gastric activity. Occasionally the motility after resection of the splanchnic nerves did not differ from that observed during the control period.

The vagus is considered the primary motor nerve to the stomach. Therefore, it would seem that the augmentation in gastric tonus sub-

11. Dragstedt, Lester R.: Failure of Reabsorption of Gastric and Pancreatic Juice as a Pathogenic Factor in Some Gastro-Intestinal Disturbances, Am. J. Surg. **11**:544, 1931.

12. Dragstedt, Lester R.; Montgomery, Laurence; Ellis, James C., and Matthews, Warren B.: The Pathogenesis of Acute Dilatation of the Stomach, Surg., Gynec. & Obst. **52**:1075, 1931.

13. Brunemeier, E. H., and Carlson, A. J.: Reflexes from the Intestinal Mucosa to the Stomach, Am. J. Physiol. **36**:191, 1914.

sequent to bilateral resection of the splanchnic nerves is due to the unopposed action of the vagus nerves. However, Carlson, Boyd and Pearcy [14] found that stimulation of the vagus nerve produces a motor response if gastric tonus is low and an inhibitory response if it is high. McCrea, McSwiney and Stopford [15] also concluded that the primary effect of stimulation of the vagus is dependent on the existing condition of the peripheral mechanism or tonus. Either inhibition or augmentation of gastric tonus may result. Hence, the type and duration of motility depend largely on the degree of gastric tonus exhibited on the day of observation.

In some instances, dogs with the splanchnic nerves sectioned showed no greater tonus and no greater rate and persistence of contractions than did the dogs with these nerves intact.[9] These observations are in keeping with our findings. In certain experiments we observed that gastric motility was more persistent during the control period. Carlson's explanation for this is that section of these nerves eliminates one of the least important of the factors involving the motor activity of the empty stomach. The conditions influencing the stomach through the blood [16] and through the vagi are still subject to practically the same variations as in the normal subject with the splanchnic nerves intact.

Cannon [17] reported that resection of the splanchnic nerves did not alter the gastric movements in the cat. It is difficult to account for this in view of our findings and those of other investigators.

After resection of the left splanchnic nerves we observed that gastric motility was at times continuous throughout a period of observation of from four to five hours. There was also an augmentation in gastric tonus but no appreciable change in the duration of and the interval between contractions. Gastric tetany was frequently observed. After resection of the right splanchnic nerves, the results simulated closely those observed subsequent to the first operation. The periods of activity were equally persistent.

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14. Carlson, A. J.; Boyd, T. E., and Pearcy, J. F.: Studies on the Visceral Sensory Nervous System: Innervation of the Cardia and the Lower End of the Esophagus in Mammals, Am. J. Physiol. **61**:14, 1922; Studies on the Visceral Sensory Nervous System: Reflex Control of the Cardia and Lower Esophagus in Mammals, Arch. Int. Med. **30**:409 (Oct.) 1922.

15. McCrea, E. D.; McSwiney, B. A., and Stopford, J. S. B.: Effect on the Stomach of Stimulation of the Peripheral End of the Vagus Nerve, Quart. J. Exper. Physiol. **15**:201, 1925.

16. Luckhardt, A. B., and Carlson, A. J.: On the Chemical Control of the Gastric Hunger Mechanism, Am. J. Physiol. **36**:37, 1914.

17. Cannon, Walter B.: Motor Activities of the Stomach and Small Intestines After Splanchnic and Vagus Section, Am. J. Physiol. **17**:429, 1906.

The gastric motor mechanism is frequently augmented in severe uncontrolled diabetes. This observation was made by Luckhardt [18] on untreated diabetic dogs and on man. In the preinsulin days Allen [19] observed that the polyphagia of diabetes in man often disappeared simultaneously with the disappearance of acidosis and glycosuria. These clinical and laboratory data indicate that there exists a relationship between gastric motility and the blood sugar level.

Bulatao and Carlson [20] found that the gastric hypermotility of diabetic dogs often disappeared when the blood sugar level was restored to normal by insulin therapy. These authors suggested the possibility that under ordinary conditions gastric tonus and the contractions of the empty stomach increase parallel with the reduction of glycogen in the tissues.

The blood sugar level of our patient was well controlled by careful therapy with insulin and dextrose. Occasionally hypoglycemia was observed, but the condition was rectified as soon as it became apparent. Stability of the blood sugar level was of paramount importance in order that the true results of splanchnic resection would not be obscured.

Alvarez [21] reported that after resection of the splanchnic nerves in rabbits the bowel became so sensitive that when it was touched it often contracted to form a firm white cord. Although gastric hypermotility was the predominant feature following bilateral resection of the splanchnic nerves in this patient, clinically there were no untoward manifestations. The postoperative course of this patient, like that of others,[22] was entirely uneventful. There was no evidence of abdominal distress, cramping sensations or colic.[23] Diarrhea was not observed. After each stage there was a lowering of the blood pressure. This was most marked after the first stage. It produced no complications. Although there has ensued a definite reduction of the requirement of insulin, up to the present time insulin cannot be wholly omitted. The effect of bilateral splanchnic resection on the diabetes will be reported in extenso subsequently.

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18. Luckhardt, A. B.: The Cause of the Polyphagia of Pancreatic Diabetes, Am. J. Physiol. **33**:315, 1914.

19. Allen, F. M.: Studies Concerning Diabetes, J. A. M. A. **63**:939 (Sept. 12) 1914; Prolonged Fasting in Diabetes, Am. J. M. Sc. **150**:480, 1915.

20. Bulatao, E., and Carlson, A. J.: The Influence of Experimental Changes in the Blood Sugar Level on Gastric Hunger Contractions, Am. J. Physiol. **69**:107, 1924.

21. Alvarez, W. C.: Effect of Degenerative Section on the Vagus and Splanchnic Nerves on the Digestive Tract, Proc. Staff Meet., Mayo Clin. **4**:205, 1929.

22. Craig and Brown.[3] de Takáts and Fenn.[6b]

23. Ivy, A. C.: The Applied Physiology of Gastro-Intestinal Innervation, Am. J. Digest. Dis. & Nutrition **1**:845 (Feb.) 1935.

CONCLUSIONS

Bilateral resection of the splanchnic nerves was performed on a patient with severe diabetes. Observations on the gastric motor mechanism revealed that after bilateral resection of the splanchnic nerves there ensued: (1) hypermotility of the empty stomach as observed by the balloon method, (2) an augmentation of gastric tonus, (3) an increase in the amplitude of contractions, and (4) no untoward gastrointestinal symptoms.

LACTOGENIC SUBSTANCE IN THE HUMAN BREAST

ITS USE IN EXPERIMENTAL STIMULATION OF MAMMARY SECRETION AND ITS ASSAY IN CASES OF CYSTIC DISEASE

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That there exists a relationship between the anterior lobe of the hypophysis and lactation has been shown by the work of Grüter and Stricker.[1] Investigations which demonstrated the effect of extracts of the anterior lobe of the hypophysis on mammary secretion have been made by Corner,[2] Nelson and Pfiffner,[3] Gardner and Turner[4] and Riddle, Bates and Dykshorn.[5] These studies have shown that when the mammary glands of rats, guinea-pigs, rabbits and dogs have been stimulated by the injection of ovarian hormones, injections of extracts of the anterior lobe of the hypophysis may initiate secretory activity.

Purified lactogenic substances have been prepared from the anterior lobe of the hypophysis by Turner[6] and his co-workers and by Riddle and his co-workers. The use of these extracts and the response of the

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2. Corner, G. W.: The Hormonal Control of Lactation, Am. J. Physiol. **95**: 43, 1930.

3. Nelson, W. O., and Pfiffner, J. J.: An Experimental Study of the Factors Concerned in Mammary Gland Growth and Milk Secretion, Proc. Soc. Exper. Biol. & Med. **28**:1, 1930.

4. Gardner, W. U., and Turner, C. W.: The Function, Assay and Preparation of Galactin, a Lactation Stimulating Hormone of the Anterior Pituitary, and an Investigation of the Factors Responsible for the Control of Normal Lactation, Research Bulletin 196, Agricultural Experiment Station, University of Missouri, June 1933.

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6. Turner, C. W.: Personal communication to the authors.

crop of the pigeon as a method of bio-assay opened new fields for the investigation of the physiology and pathology of lactation in human beings.

Kurzrok and his associates [7] have reported on the clinical use of lactogenic substance in thirty-seven women who had been delivered of normal children. Twenty-nine of these women were thought to have insufficient milk. Twenty-one of these showed an increase in the amount of milk after the sixth day post partum, when from 75 to 400 birds units of lactogenic substance was injected intramuscularly. In four of the eight remaining women only a moderate response was noted, and in four no response was observed. In eight normal women in whom the secretion was normal, no response was noted after the use of the lactogenic substance.

Werner [8] gave injections of lactogenic substance (200 bird units daily for from four to fourteen days) to ten castrated women, ranging in age from 21 to 35 years. The breasts were prepared by injections of estrogenic substance to which was added the gonadotropic factor from the urine of pregnant women or progestin in eight cases. All noted enlargement or engorgement of the breast which might be regarded as suggesting the onset of lactation. Lactation did not occur, however, in any case. Anaphylactic reactions were noted in three.

In an experimental study in which an attempt was made to reproduce cystic disease and benign tumors of the breast (Geschickter, Lewis and Hartman [9]) injections of estrogenic substance followed by injections of lactogenic substance were given to four male monkeys and one female monkey. Secretion occurred in the female but not in the males (fig. 1). The female was an adult menstruating macacus and had received 500 units of estrogenic substance, followed by the injection of 400 units of lactogenic substance over a period of five days.

Allen, Gardner and Diddle [10] were able to produce lactation in five mature female monkeys by injecting lactogenic substance. Two of these animals had had previous injections of estrogenic substance.

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7. Kurzrok, R.; Bates, R. W.; Riddle, O., and Miller, E. G., Jr.: The Clinical Use of Prolactin, Endocrinology **18**:18, 1934.

8. Werner, A. A.: Experiment to Produce Lactation in Castrate Women, Endocrinology **19**:144, 1935.

9. Geschickter, C. F.; Lewis, D., and Hartman, C. G.: Tumors of the Breast Related to the Oestrin Hormone, Am. J. Cancer **21**:828, 1934.

10. Allen, E.; Gardner, W. U., and Diddle, A. W.: Experiments with Theelin and Galactin on Growth and Function of the Mammary Glands of the Monkey, Endocrinology **19**:305, 1935.

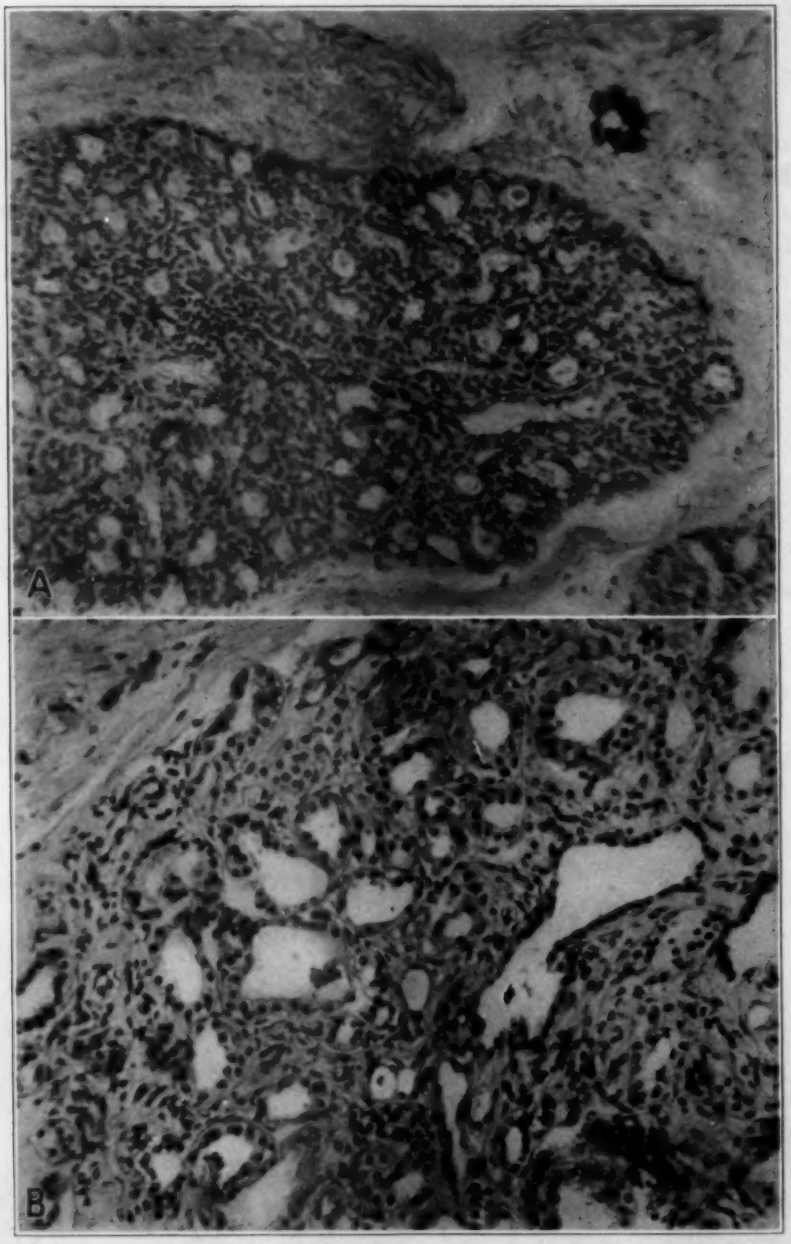

Fig. 1.—Photomicrographs of specimens from the breast of a mature female monkey (*A* before and *B* after treatment) which was given injections of 500 rat units of estrogenic substance followed by 400 bird units of lactogenic substance (given twice daily over a period of five days). Mammary secretion (lactation) occurred.

Fig. 2.—Photomicrographs of specimens from the breast of a male monkey on the sixth day (*A*) and on the twenty-third day (*B*) after a course of ten injections of lactogenic substance given twice daily for a period of five days. The monkey had been previously subjected to experimental gynecomastia by injections of 2,200 rat units of estrogenic substance over a period of six weeks.

EFFECT OF LACTOGENIC SUBSTANCE ON THE MAMMARY GLANDS OF MENSTRUATING WOMEN

Liquefaction of the periductal fibrous tissue and shedding of the epithelial elements were observed microscopically in the breasts of monkeys after injections of lactogenic substances.[11] Like injections were given menstruating women who had various forms of chronic mastitis but who had not been recently delivered. The studies differed, therefore, from those which had previously been made. In two instances a biopsy of tissue from the breast was made both before and after the injections, and in three cases, after the injections had been given. In all, fourteen women received injections. Mammary secretion occurred in three after injections of estrogenic substance [11] and lactogenic substance. No secretion was noted in six patients who received estrogenic and lactogenic substances.

TABLE 1.—*Administration of Estrogenic and Lactogenic Substances with the Production of Mammary Secretion*

					Estrogenic Substance		Lactogenic Substance	
Case	Patient	Age, Years	Previous Pregnancy	Diagnosis	Dose, Rat Units	Total Rat Units	Dose, Bird Units	Total Bird Units
1	M. P.*	30	1 (10 yrs.)	Adenosis	500 every 4th day	3,500	160 daily for 5 days	800
2	M. L. H.	46	1 (23 yrs.)	Adenosis	500 every 4th day	3,500	80 twice daily for 7 days	1,120
3	A. B. N.†	40	1 (10 yrs.)	Adenosis	500 every 4th day	3,000	100 twice daily for 3 days	600

* Two biopsies were made three and eleven days after the onset of the secretion.
† Two similar courses of estrogenic and lactogenic substances were given in September 1934 and in January 1935, but no secretion was produced. The third course, noted above, was given in April 1935.

Five of the women who were given only lactogenic substance had no secretion. A Negro with gynecomastia and a Negress who had hyperthyroidism received both estrogenic substance and lactogenic substance, but neither showed any evidence of mammary secretion (tables 1 to 3).

This is a small series, but the results indicate that the injection of lactogenic substance may cause mammary secretion in nonpregnant women when they have been previously stimulated with estrogenic substance. In the three cases in which secretion was noted (table 1) from 3,000 to 3,500 rat units of estrogenic substance (from 24,000 to 28,000 international units) was administered. In each instance estrogenic substance was given intramuscularly before the menstrual period,

11. Drs. J. F. Anderson and J. A. Morrell, of E. R. Squibb & Sons, supplied the estrogenic substance (amniotin) and the lactogenic substance (prolactin) used in these studies.

TABLE 2.—*Administration of Estrogenic and Lactogenic Substances Without the Production of Mammary Secretion*

Case	Patient	Age, Years	Previous Pregnancy	Diagnosis	Estrogenic Substance: Dose, Rat Units	Estrogenic Substance: Total Rat Units	Lactogenic Substance: Dose, Bird Units	Lactogenic Substance: Total Bird Units
1	M. T.*	38	None	Fibro-adenoma	500	500	20 twice daily for 5 days	200
2	J. D.†	18	None	Virginal hypertrophy	1,000 weekly for 5 wks.	5,000	120 every 3d day	720
3	P. L.‡	42	1 (7 yrs.)	Dilated ducts beneath nipple	500 daily for 5 days	2,500	50 twice daily for 4 days	320
4	D. B.	35	None	Virginal hypertrophy	500 twice monthly for 3 mos.	3,000	40 once	40
5	M. T.	25	None	Fibro-adenoma	1,000 once	1,000	60 daily for 5 days	300
6	M. J.	29	1 (7 yrs.)	Virginal hypertrophy	1,000 twice	2,000	60 daily for 13 days	780
7	M. W.* male	18	.....	Gynecomastia	1,000 once	1,000	20 twice daily for 5 days prior to injection of estrogenic substance; 40 daily for 8 days after injection of estrogenic substance	520
8	L. B.	25	2 (7 and 9 yrs.)	Hyper-thyroidism	500 daily for 6 days	3,000	80 twice	160

* A specimen was obtained for biopsy.
† Three weeks elapsed after the last injection of estrogenic substance and the first injection of lactogenic substance.
‡ This patient had a previous course of injections of estrogenic substance one month prior to the injections of estrogenic and of lactogenic substance, which were given simultaneously. A biopsy was made before the course of these combined injections and another biopsy afterward.

TABLE 3.—*Administration of Lactogenic Substance Without the Production of Mammary Secretion*

Case	Patient	Age, Years	Previous Pregnancies	Diagnosis	Lactogenic Substance: Dose, Bird Units	Lactogenic Substance: Total Bird Units
1	C. S.*	49	7	Fibro-adenomatous	60 or 40 once daily for 17 days	740
2	E. E.†	34	1	Cystic disease of breast	30 twice daily for 7 days	420
3	A. S.‡	36	3	Adenosis	80 daily for 4 days	320
4	I. J.	26	None	Adenosis	80 daily for 8 days	640
5	L. S.	21	None	Virginal hypertrophy	80 daily for 6 days	480

* A specimen was taken for biopsy.
† An anaphylactic reaction was observed.
‡ This patient was given a course of estrogenic substance two months previously, 500 rat units being given weekly (a total of 2,500 rat units).

and the injections were discontinued during menstruation. Injections of lactogenic substance were started the day after menstruation ceased and were given intramuscularly within a week, the amount given ranging from 600 to 1,120 rat units at the time secretion appeared.

The appearance of secretion was preceded by a feeling of engorgement and heaviness of the breasts and accompanied by an increase in their size. The secretion was creamy white and in no case lasted longer than three days. No more than 10 or 12 drops could be expressed from the nipple at any time. In two cases secretion was obtained from both breasts, and in the third case, from the left breast only. Secretion ceased spontaneously in all cases. Cessation of the secretion occurred in two cases even when lactogenic substance was administered after the secretion appeared and the nipples were stimulated by the patient. In one

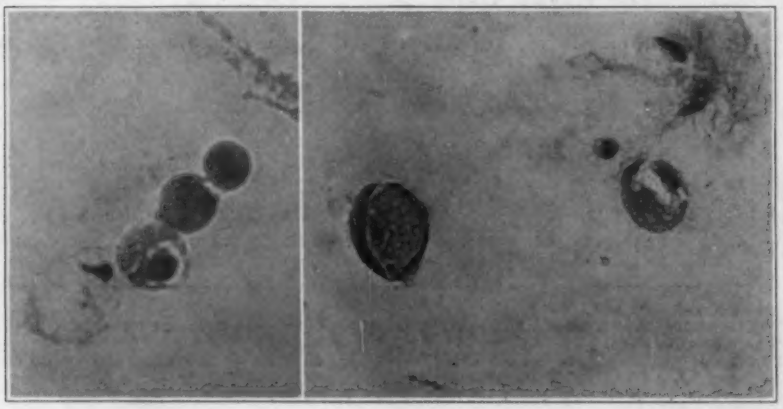

Fig. 3 (case 1, table 1).—Photomicrograph of mammary secretion obtained after the patient had received 3,500 rat units of estrogenic substance, followed four days later by 800 bird units of lactogenic substance (160 bird units once daily for five days).

case the breast pump was used, but the period of secretion was not prolonged. In this case two courses of injections of lactogenic substance similar to those given in the third course had been administered seven and four months before without resulting in the appearance of secretion.

Microscopically (fig. 3) the secretion in all the cases resembled colostrum, fatty droplets and desquamated cells being found. In case 1 (table 1) a biopsy was performed on the third day after the appearance of the secretion, and another biopsy of tissue from the opposite breast was made eleven days after the secretion first appeared. Microscopic examination of the tissue revealed hypertrophy and an increase in the number of cells lining the lactiferous tubules and an increase in the

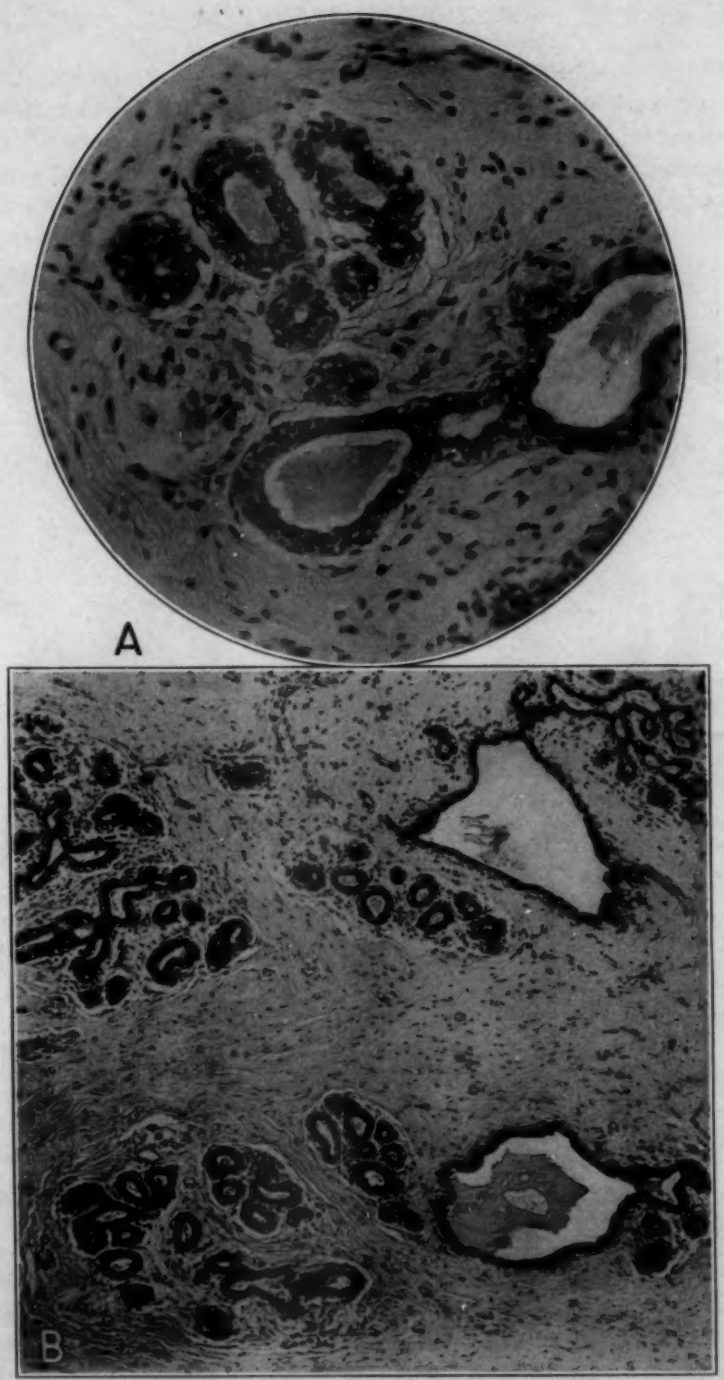

Fig. 4 (case 1, table 1).—Photomicrographs of specimens removed for biopsy on the third day (*A*) and on the eleventh day (*B*) after the appearance of mammary secretion. The terminal tubules are dilated and widely separated. Secretion is visible in the lumens of the tubules.

amount of periductal connective tissue. Both these changes (on the basis of work previously reported) may be interpreted as response to estrogenic substance. In addition, maturation and secretory activity in the epithelium of the lobules, accumulated secretion and desquamated cells within the lumens were noted. These changes, together with the

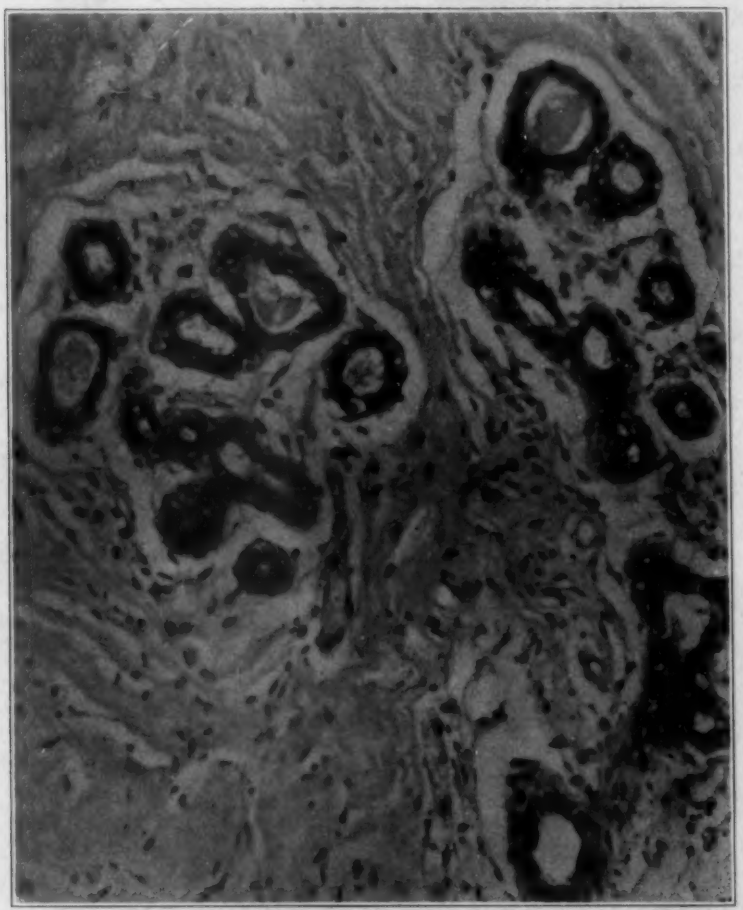

Fig. 5 (case 3, table 2).—Photomicrograph of a specimen obtained for biopsy after the injection of 5,500 rat units of estrogenic substance. The tissue was removed in conjunction with an exploration for dilated ducts beneath the nipple. Note the hypertrophy and dilatation of the terminal tubules and the periductal hyperplasia. Secretion is seen in the lumen.

loose, edematous appearance of the periductal tissue, were interpreted as having been caused by the injections of lactogenic substance. They were noted in both biopsy specimens, although there had been no demonstrable secretory activity for eight days preceding the last biopsy. These

changes were noted also in case 3 (table 2) after injections of estrogenic and lactogenic substances, although there had been no evidence of mammary secretion and no milk could be expressed from the nipple (figs. 5 and 6).

True lactating acini were not observed, although serial sections were made. Evidences of secretory activity seemed to be confined to the terminal tubules of the rudimentary acini, which were dilated and widely separated by the edematous periductal connective tissue. It is possible that scattered functioning acini were responsible for the secretion but were not included in the tissue removed for biopsy.

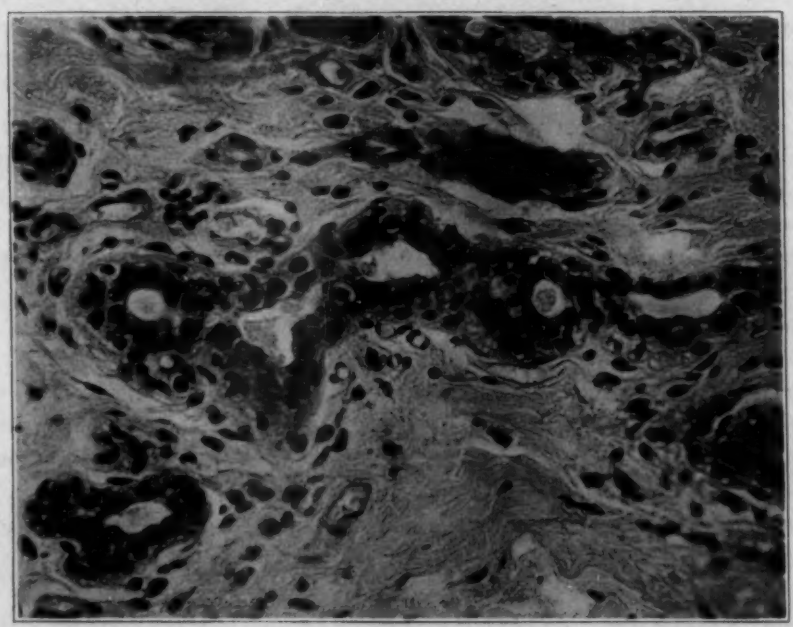

Fig. 6 (case 3, table 2).—Photomicrograph of tissue obtained for a second biopsy, approximately six weeks after the tissue shown in figure 5 was removed. During the five preceding days the patient had had daily injections which constituted a total dose of 2,500 units of estrogenic substance and 320 bird units of lactogenic substance.

Large doses of estrogenic substance with smaller doses of lactogenic substance or lactogenic substance given weeks after estrogenic substance had been administered failed to produce definite gross secretion. In the group of cases in which estrogenic substance in amounts varying from 500 to 5,000 rat units (4,000 to 40,000 international units) was given intramuscularly, there were six females who were known to have conditions of the breast of the type associated with an increased amount of the estrogenic principle (fibro-adenoma; virginal hypertrophy).

The lactogenic substance in these cases was given in small amounts (40 to 320 bird units), except in two cases. In the case in which 5,000 rat units of estrogenic substance and 720 bird units of lactogenic substance were given (case 2, table 2) the lactogenic substance was administered only every third day over a period of seventeen days, and an interval of three weeks elapsed between the last injection of estrogenic substance and the first injection of lactogenic substance. In the case in which 320 bird units of lactogenic substance was given (case 3, table 2) the lactogenic substance was given at the same time as the estrogenic substance. A biopsy was made before and after the injections. Microscopically some evidences of secretory activity were noted. In case 6 (table 3) no secretion was observed, although 2,000 rat units of estrogenic substance and then 780 bird units of lactogenic substance were given.

In the patient with gynecomastia a blood test showed the presence of the estrogenic substance, and a biopsy was made before and after the injections. This patient received 200 bird units of lactogenic substance between April 18 and April 25, 1,000 rat units of estrogenic substance on April 25 and 320 bird units of lactogenic substance between April 26 and May 26. The breast became enlarged and tense, but no secretion was noted (figs. 7 and 8).

Rather large doses of lactogenic substance (320 to 740 bird units) were given to women during the menstrual cycle, when supposedly normal amounts of estrogenic substance should be present, but no mammary secretion was noted. Five women had normal menstrual cycles, and injections of lactogenic substance were made on successive periods of seventeen, seven and four days, respectively. In case 1 a biopsy was made before and after the course of injections (fig. 9).

Although true functional lactation was not observed, the secretory activity obtained with estrogenic and lactogenic substances indicates that lactogenic substance represents the hormone of the anterior lobe of the pituitary body which stimulates human mammary secretion. This is also suggested by bio-assays of fluid obtained from blue dome cysts in patients with chronic cystic mastitis. In many cases of cystic mastitis a substance may be found which when injected into pigeons produces a typical response in the crop. This response is identical with that obtained after injections of lactogenic substance which has been prepared from beef pituitary glands (beef pituitary glands were the source of the lactogenic substance used in the investigations forming the basis of this report). Further evidence is supplied by the results obtained by Kurzrok,[7] which showed an increase in the lactation of women post partum in response to injections of lactogenic substance. The failure of Werner[8] to secure secretion in his series of castrated women was

probably due to depletion of the estrogenic substance in the tissues. Judging from the results obtained for castrated rats, far more estrogenic substance (about fifteen times as much) is needed to prepare the breast for lactogenic substance in castrated women than in noncastrated women. The maximum dose used by Werner was 13,200 rat units. The dose calculated on the basis of the present series for castrated women is in the neighborhood of 45,000 or 50,000 rat units. Moreover, in these women there is a similar depletion of progestin, which probably is not compensated for by the small injections given in two cases in Werner's series.

Fig. 7.—This Negro with gynecomastia received a course of injections consisting of 200 bird units of lactogenic substance for a period of five days, 1,000 rat units of estrogenic substance on the sixth day and 320 bird units of lactogenic substance during the next fifteen days.

Lactogenic substance can be demonstrated both in the mammary tissue and in the colostrum of normal lactating cows. We have assayed the udders of lactating cows in three instances.[12] Two of the animals were killed ten days and one was killed two days after the last milking. In all three instances the extract prepared from udder tissue showed the presence of lactogenic substance when tested on the crops of pigeons. We have been able to demonstrate the presence of lactogenic substance

12. Dr. and Mrs. George O. Gey, of this laboratory, cooperated in the extraction of udders and colostrum for lactogenic substance.

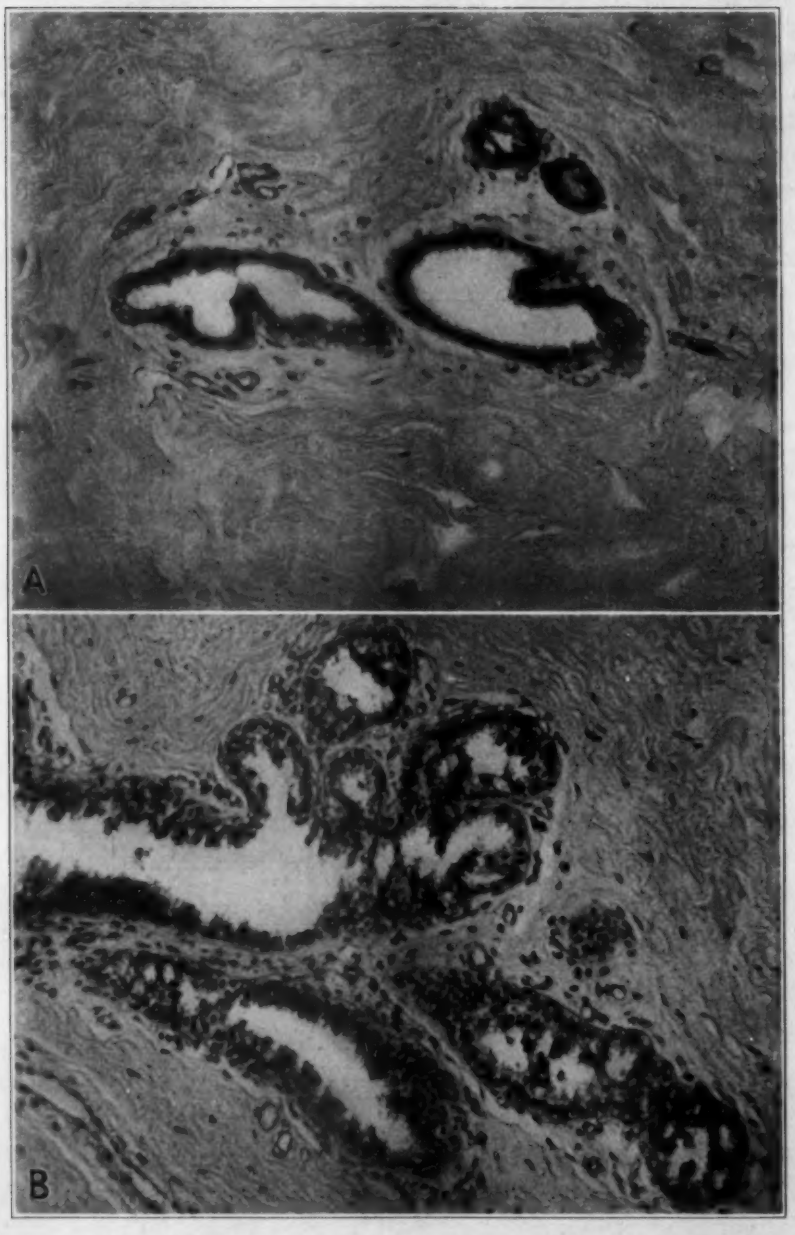

Fig. 8.—*A*, a specimen taken for biopsy before the injection of lactogenic substance; *B*, after the injections, in the Negro shown in figure 7.

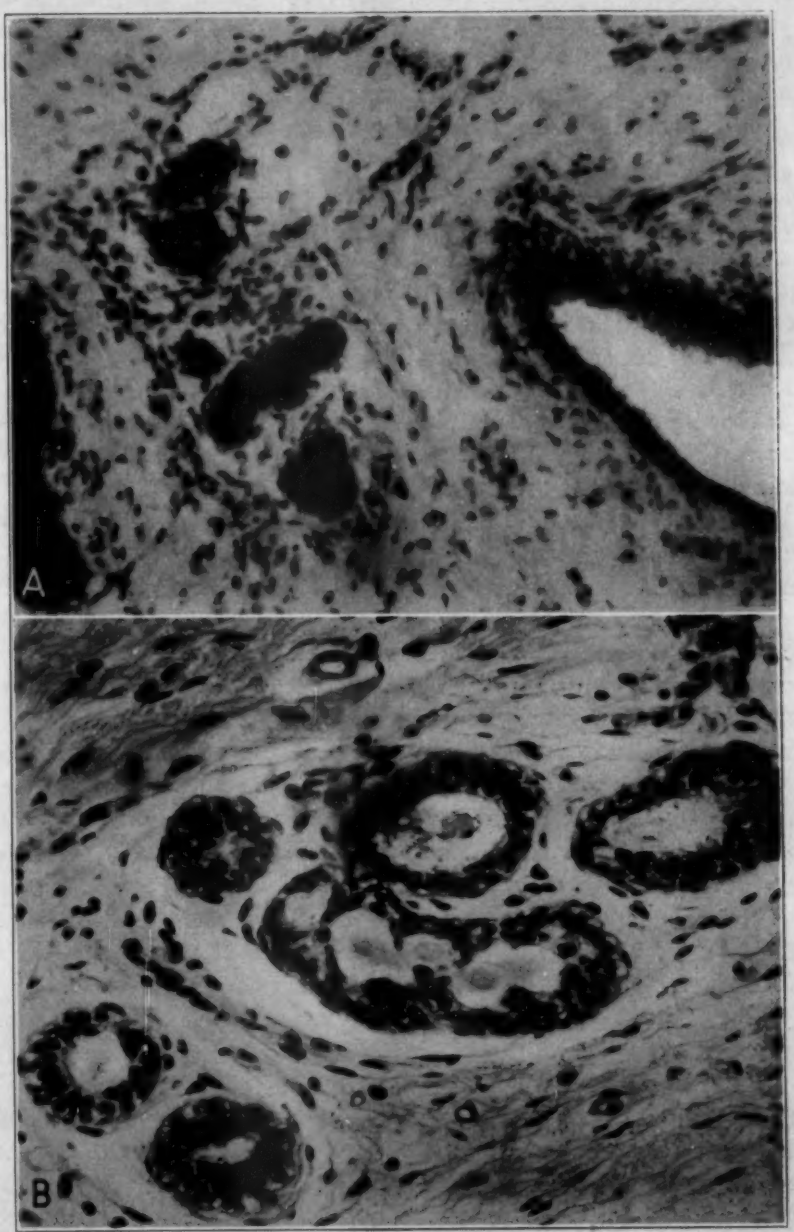

Fig. 9 (case 1, table 3).—*A*, tissue from a woman with fibro-adenoma of the breast after four injections of lactogenic substance. *B*, a biopsy specimen obtained one month later from the opposite breast after daily injections of lactogenic substance over a period of seventeen days, making a total of 740 bird units.

also in the milk mixed with colostrum from lactating cows within the first two weeks of calving. Whole milk obtained at varying periods after an interval of two weeks after calving, however, showed no lactogenic substance. Perhaps the lactogenic substance present in colostrum may play a part in the formation of the witch's milk of nursing infants.

However, it is apparent that lactogenic substance alone or in combination with estrogenic substance does not produce true lactation. Lactogenic substance is not peculiar to lactating animals or to females, since the pituitary glands obtained from castrated bulls (ordinary beef pituitary glands) are a potent source of this hormone. Turner [6] has been able to demonstrate traces of lactogenic substance in the blood and urine of nonlactating cows. Both estrogenic substance and lactogenic substance can be demonstrated in the breasts of human females with chronic cystic mastitis, which is particularly frequent in childless women. The rôle which these hormones may play in the causation of cystic disease is discussed subsequently.

The fact that mammary secretion was stimulated by injections of estrogenic and of lactogenic substance in the three cases listed in table 1 does not indicate that these two hormones alone are sufficient for lactation or the secretion of colostrum. In all three of the patients the breasts were under the influence also of progestin, a hormone from the corpus luteum. These patients had the form of chronic cystic mastitis which we [13] have termed adenosis, in which the breast is under the influence of increased stimulation by progestin. This is manifested pathologically by proliferation of acinar elements and minute papillomas, which is characteristic of all cases of adenosis. The administration of estrogenic and lactogenic substances in these cases apparently completes the physiologic cycle and causes mammary secretion.

These studies therefore suggest that both estrogenic substance and progestin are essential in the preparation of the human breast before an adequate response to lactogenic substance can occur. It is to be noted, however, that lactogenic substance was not effective when given simultaneously with estrogenic substance.

There is additional evidence for concluding that large amounts of both hormones when present simultaneously may be antagonistic in their influence on the breast. In treating women with blue dome cysts of the breast or with galactorrhea which has been present for years it has been found that the administration of large doses of estrogenic substance (1,000 rat units administered every other day for a period of two weeks) will inhibit the secretory activity of the breast and in some instances will cause the disappearance of the palpable cyst. Moreover, in assaying

13. Lewis, D., and Geschickter, C. F.: Ovarian Hormones in Relation to Chronic Cystic Mastitis, Am. J. Surg. **24**:280, 1934.

the fluid recovered by aspiration from untreated blue dome cysts it has been found that while either estrogenic or lactogenic substance may be present in high concentrations, the fluid from a single cyst has not been found to contain both hormones. There was one exception, but in that case the content of estrogenic substance was high and concentration of lactogenic substance was low (table 4).

The treatment of adenosis of the breast in the three cases listed in table 1 by the administration of estrogenic and lactogenic substances

TABLE 4.—*Assays of Tissue and Fluid from Patients with Cystic Disease of the Breast for Lactogenic and Estrogenic Substances*

Specimen	Patient	Hormone Assayed	Result of Bio-Assay
			Bird Units per Liter
Cyst fluid*	S. K.	Lactogenic substance	2,000
	L. F.	Lactogenic substance	720
	Bur.	Lactogenic substance	0
	Jar.	Lactogenic substance	250
	Car.	Lactogenic substance	100
	Gar.	Lactogenic substance	750
	N. W.	Lactogenic substance	250
	Grom.	Lactogenic substance	250
			Rat Units per Liter
Cyst fluid†	B. C. ‡	Estrogenic substance	6,000
	Jar.	Estrogenic substance	0
	Car.	Estrogenic substance	2,000
	Gar.	Estrogenic substance	0
	N. W.	Estrogenic substance	0
			Rat Units per Kilogram
Mammary tissue	N. B.	Estrogenic substance	6,000
	R. C.	Estrogenic substance	1,000
	P. D.	Estrogenic substance	200
	I. D.	Estrogenic substance	4,000
	Bro.	Estrogenic substance	0
	A. L.	Estrogenic substance	0
	Bur.	Estrogenic substance	0

* Tested by the response in the crops of pigeons (Riddle test).

† Tested by vaginal smear in castrated rats (Allen-Doisy test).

‡ Fluid was removed from cysts of both breasts of this patient. The milky fluid from the right breast contained 6,000 rat units of estogenic substance per liter. The yellow turbid fluid from the left breast did not contain estrogenic substance.

resulted in the cure of two of the patients and marked improvement in the third for a period of more than a year after the cessation of treatment. The breasts were painful before menstruation and contained multiple indefinite nodules and usually one or more caked areas. They became less painful and lumpy after injections of estrogenic substance (1,000 rat units twice weekly). Patients with this condition, who are usually apprehensive and underweight and often have a palpable thyroid gland, are markedly benefited by treatment with estrogenic substance; but there is difficulty in maintaining this marked clinical improvement

in some cases by the use of estrogenic substance alone, judging by the twenty patients treated with estrogenic substance only. In the patients who received estrogenic plus lactogenic substance the results noted from six to eighteen months after the cessation of therapy were more striking than those in the patients who received estrogenic substance only.

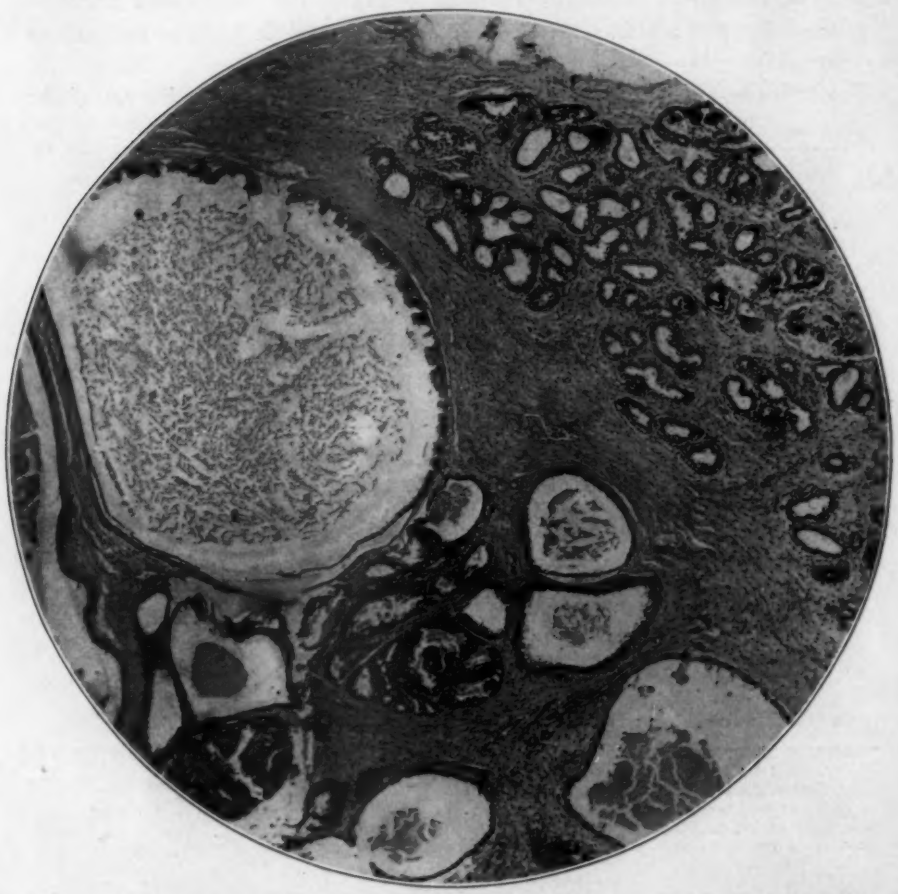

Fig. 10.—Photomicrograph showing epithelial hypertrophy, cyst formation and secretion in a case of cystic disease of the breast. The pathologic process resembles pseudolactation with colostrum formation.

On the basis of results obtained thus far, large doses of estrogenic substance alone are worthy of trial to control the formation of cysts in patients with cystic disease of the breast, and the administration of estrogenic substance plus lactogenic substance is indicated in cases of adenosis.

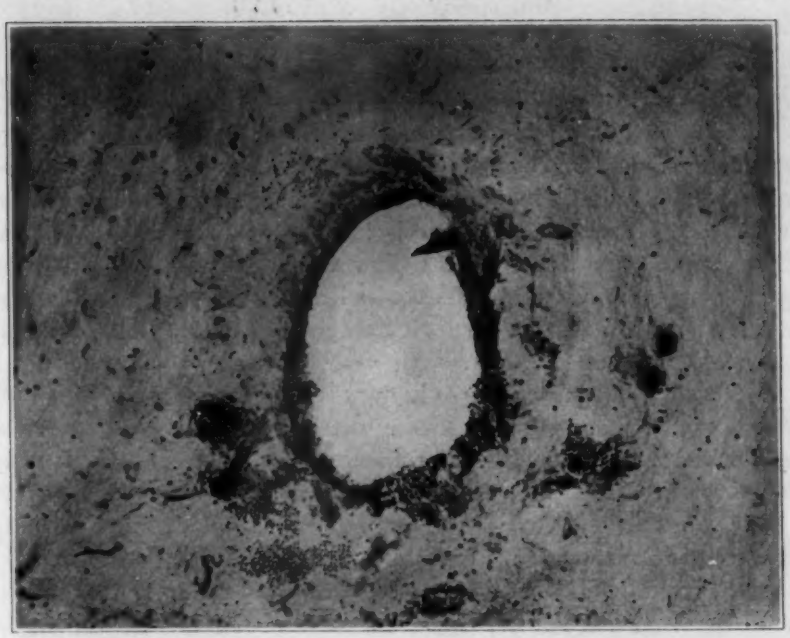

Fig. 11.—Photomicrograph of tissue from the wall of a blue dome cyst. The fluid from the cyst was assayed for lactogenic substance and contained 2,000 bird units per liter.

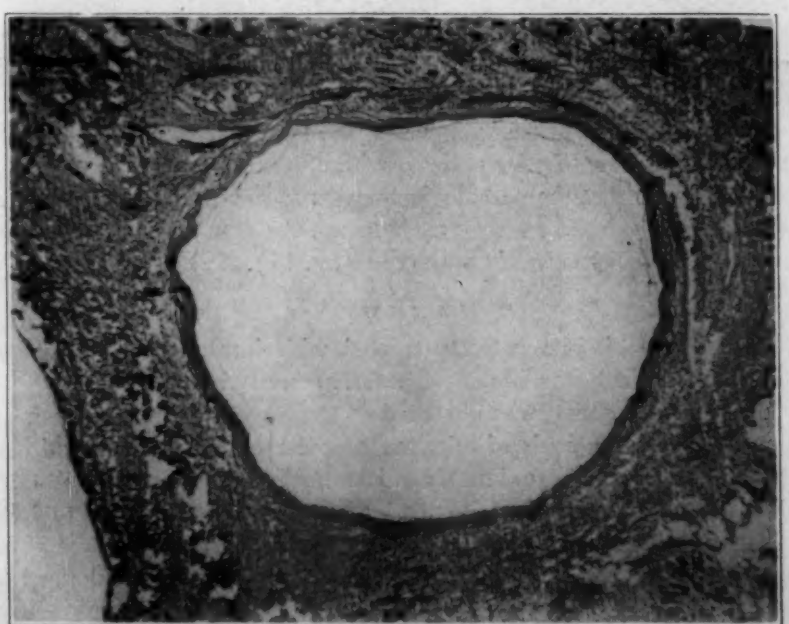

Fig. 12.—Photomicrograph of tissue removed from a patient with cystic disease of the breast. Assay for estrogenic substance showed 6,000 rat units per kilogram of tissue.

BIO-ASSAY FOR LACTOGENIC SUBSTANCE IN CASES OF CYSTIC DISEASE OF THE BREAST

With regard to cystic disease of the breast, which is a relatively common condition in childless women approaching the menopause, a serous or milky discharge was observed in 3 per cent of a series of five hundred patients studied in this laboratory. The content of such cysts at operation or aspiration usually reveals a cloudy or milklike fluid. Microscopic examination of the excised mammary tissue surrounding the blue dome cyst shows pathologic changes which may closely simulate physiologic lactation (fig. 10).

Because of these findings we have assayed cyst fluid and mammary tissue obtained from patients with cystic disease and have found that they contain estrogenic and lactogenic substances (table 4). These assays show that the cloudy milklike fluid may contain high concentrations of these substances (lactogenic substance up to 2,000 bird units per liter and estrogenic substance up to 6,000 rat units per kilogram; fig. 11). The fluid from a single cyst, however, with one exception has not been found to contain both hormones. In view of the fact that a similar milklike secretion can be obtained by the injection of estrogenic substance and lactogenic substance in menstruating women, it seems reasonable to conclude that these hormones are responsible for the pathologic secretion observed in cases of cystic disease.

We have assayed the mammary tissue of patients with cystic disease for lactogenic substance with positive results in one case. In view of the fact that this hormone has been obtained by us from the mammary tissue of cows and that by bio-assays we have found estrogenic substance in the mammary tissue of four patients with cystic disease, it seems reasonable to conclude that the pathologic changes observed in the surrounding tissues as well as the secretory changes are the result of stimulation by the estrogenic and lactogenic hormones (fig. 12).

SUMMARY

A series of sixteen patients treated with intramuscular injections of estrogenic and lactogenic substances has been studied.

Mammary secretion was observed in three menstruating women for whom a clinical diagnosis of adenosis of the breast was made and each of whom received approximately 3,500 units of estrogenic substance over a period of a month, followed by injections of from 600 to 1,120 bird units of lactogenic substance given within a week. The secretion ceased within a period of three days and could not be prolonged by further injections or by mechanical stimulation.

Histologic studies of tissue removed for biopsy were made before and after the injections of several cases. The changes of true functional lactation were not observed histologically.

Bio-assays showed the presence of lactogenic substance in the tissue of udders from lactating cows and in the milk (mixed with colostrum) of lactating cows obtained within two weeks of calving. It was concluded that high concentrations of estrogenic and lactogenic substances and of progestin are probably essential to normal lactation in the human breast.

The resemblance between the secretory activity seen in patients with chronic cystic mastitis and that obtained in the patients treated in this series has been pointed out.

Bio-assays have demonstrated the presence of estrogenic and of lactogenic substance in the cyst fluid from patients with chronic cystic mastitis. Bio-assays have also shown the presence of estrogenic substance in mammary tissue removed from patients with chronic cystic mastitis.

It is concluded that lactogenic and estrogenic substances play an etiologic rôle in the secretory activity and in the pathologic changes observed in patients with cystic disease.

Dr. Charles W. Turner, of the University of Missouri, checked the assays for lactogenic substances.

DISTURBANCES IN GASTRO-INTESTINAL FUNCTION AFTER LOCALIZED ABLATIONS OF CEREBRAL CORTEX

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The great difficulty of keeping the totally decorticated animal in a state of suitable nutrition led us to suspect an intrinsic derangement of digestion. It was observed that operations on the frontal lobe were followed by an especially high mortality rate occurring during the third and fourth postoperative weeks. Observation of the function of the stomachs of such animals by previously made fistulas appeared to point to a disturbance of gastric motility. A thorough study of a "chronic" decorticated dog pointed toward evidence of deranged autonomic function. The present series of observations represents an attempt to investigate the phenomena of gastric motility after injury to cortical tissue of the frontal lobe by the use of the Cannon technic of direct visualization with the fluoroscope.

MATERIAL AND METHODS

Because of the carefully estimated normal standards of Cannon the cat was chosen as the experimental animal. After a variable period of preliminary observation to assure ourselves that the functions of the cats chosen for the experiment fell within the limits of variations to be expected in a normal population, the animals were subjected to localized lesion of the cortex. The case of the brain was opened, the dura was incised and the cortical tissue was removed with a curet. In order to be certain that the surgical procedure in itself was not a factor in producing the results obtained, cortical tissue other than from the frontal lobe was removed in control animals. As a check on the housing, feeding and incidentals as well as on the effect of repeated barium sulfate meals and exposure to roentgen rays, intact animals were also used as controls. The examination of the animals operated on followed the procedure of Cannon for fluoroscopic visualization of gastro-intestinal movements.

EXPERIMENTAL RESULTS

As an examination of the graphs in figure 1 indicates, there was an increase in intestinal activity beginning shortly after the operation for removal of tissue from

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the frontal lobe (operations 3, 4, 7, 8, fig. 1 and protocols). When the cortical tissue situated posteriorly was removed (no. 2 and 5, fig. 1), a temporary overactivity was observed, but this soon passed away. After the operation there was a disturbance of the number of waves present in the stomach, the rate of propagation of single waves and the number of waves passing per minute. This disturbance became more pronounced as time elapsed after the operation. Beyond this aggravation with a lapse of time, no clear correlation of these minor irregularities is apparent to us at present. Nearly all the animals ate within one hour after the operation.

The emptying time of the stomach and the twenty-four hour and forty-eight hour clearance time are fairly constant in the normal animal. Shortly after injury to the frontal lobe the emptying time of the stomach was increased. This was due to increased resistance to the passage of food through the pylorus and not to gastric hypotonia, since the stomach could be seen to be contracting more vigorously against the resistance of the sphincter.

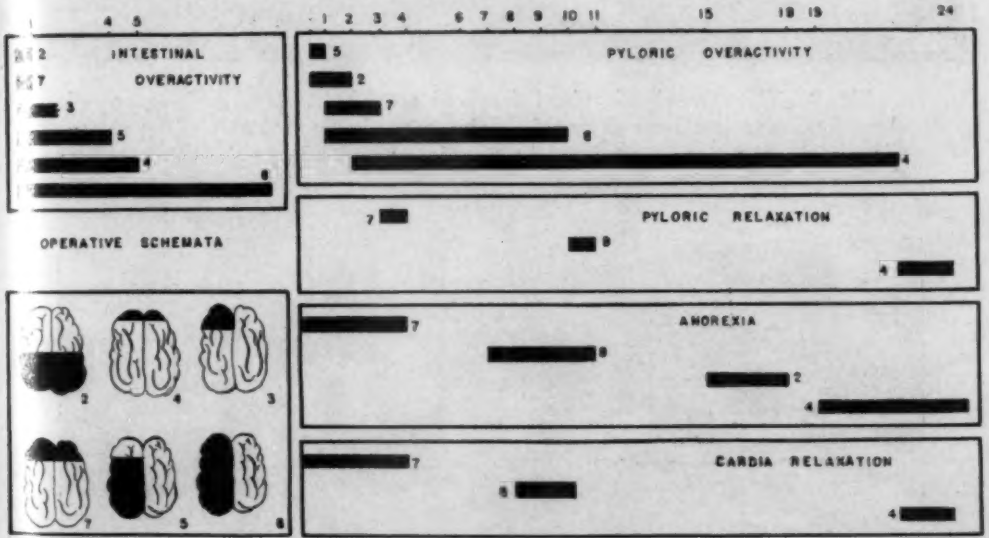

Fig. 1.—Individual block graphs indicate the observations on cats with damaged cortical tissue. The days after operation are indicated by figures across the top of the graphs. The section showing intestinal overactivity is based on the rate and amplitude of intestinal movements plus an estimation of the brevity of the intestinal segments. The section showing pyloric overactivity is based on the time of passage of the barium into the small intestine and the total emptying time of stomach. The section showing pyloric relaxation is based on observations on obvious hypotonus of the pylorus and on the emptying time of the stomach. The section showing data on anorexia is based on the failure of the animal to eat the usual diet voluntarily. The section on cardia relaxation is based on the observation that the barium would regularly ascend into the esophagus when the stomach contracted, when the animal's movements set up fluid waves or when there was moderate pressure on the abdomen. The section marked operative schemata illustrates the extent of the cortex which was removed (black). These observations were verified subsequently at autopsy. A résumé of the operative procedure on each animal is given in the tabulation preceding the protocols.

Fig. 2.—The stomach of animal 5 opened posteriorly, showing the areas of ulceration. The ulcers are arranged chiefly on the lesser curvature. The photomicrographs shown in figures 3 and 4 are made from the triangle-shaped ulcer near the middle of the lesser curvature.

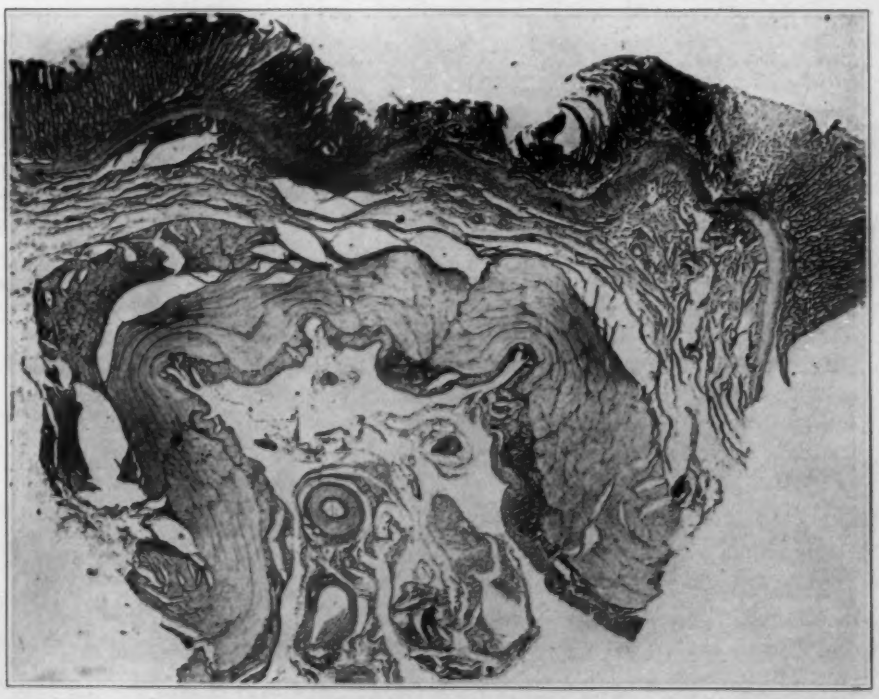

Fig 3.—Photomicrograph of the ulcer mentioned in the legend of figure 2. Laterally, intact mucosa is observed. In the center, a tuft of necrotic tissue is surrounded by a circular depressed ditch. External to the muscular coat is a somewhat thickened artery.

After a greater or lesser time (depending on the severity of the operation) the animal failed to eat voluntarily, and concomitantly with or shortly after the development of this stage of anorexia the tone of the cardiac sphincter was reduced, so that barium ascended into the esophagus on contraction of the stomach. About this time, or soon after, the condition of increased pyloric tone gave way to a decrease in pyloric tone, which fell far below normal levels. As a result, the emptying time of the stomach was reduced to a phenomenally short time (in some cases to as low as thirty minutes). Although gastric activity was somewhat decreased in this stage, the stomach was still active. In the stage of anorexia and thereafter it was necessary to feed the animals forcibly, and they soon became emaciated and died after considerable loss of weight.

The stomach was seen to be hyperemic and to present petechial hemorrhages if the autopsy was performed within about two weeks after operation. The congestion was most marked in the vicinity of the cardia. The duodenum also sometimes presented a similar picture of congestion. At later periods ulceration rather than hyperemia was present. The area of ulceration was most marked along the lesser curvature and anterior surface of the stomach (fig. 2). The ulcers were punched out and in cross-section (fig. 3) showed a circular necrotic moat, in the center of which a somewhat raised tuft of tissue showed a central artery (fig. 4), which could be seen to contain débris.

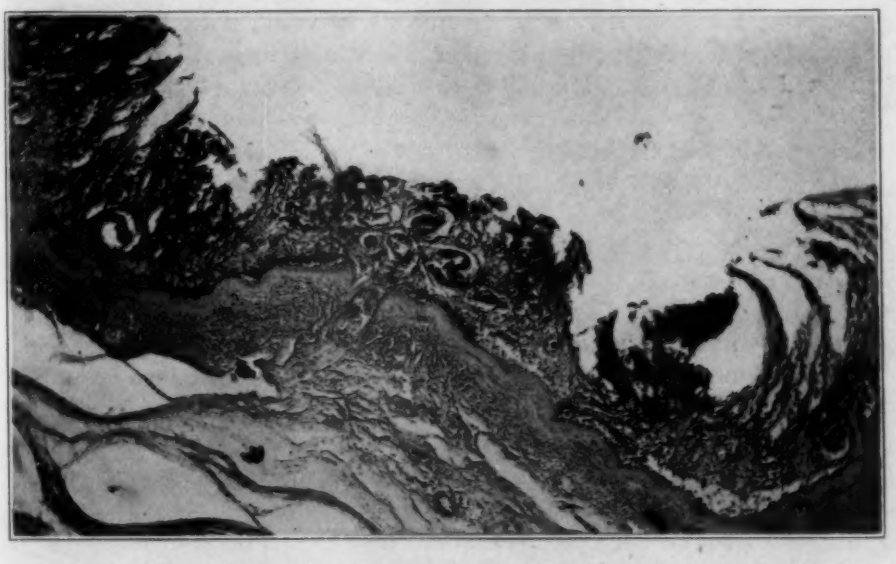

Fig. 4.—Photomicrograph of the central raised area shown in figure 3. Note the central artery entering the mucosa. It is seen to contain débris.

COMMENT

That the cortex of the frontal lobe seems to be capable of exerting an effect on gastro-intestinal activity would appear from the work of Keller,[1] who stimulated this region and observed changes in gastro-

1. Keller, A. D.; Hare, W. K., and D'Amour, M. C.: Proc. Soc. Exper. Biol. & Med. **30**:772, 1933.

intestinal activity. Watts [2] recently reported similar observations. Watts, in addition, concluded that extirpation of both premotor areas affects gastro-intestinal motility, but his presentation of experimental observations mentioned only stimulation. Stimulation experiments are open to the criticism that the current may spread to the hypothalamus. Watts apparently was relying for his evidence of the effect of extirpation on the finding of intussusception in monkeys from which the premotor area had been ablated (Watts and Fulton [3]). There can be no doubt of the value of the latter finding, which points strongly to the frontal lobe as important for gastro-intestinal motor function. The idea of neurogenic ulcers is of course not new; Keller,[1] following the lead of the Cushing school, reported the experimental production of ulcers after injury to the brain stem. In our animals, however, not only was there no injury to the hypothalamus, but injury of very small parts of the frontal lobe alone (fig. 1, no. 4) was sufficient to cause ulceration (fig. 2). It is not unlikely that the mechanism of production of the phenomena described in this paper is composed of an upper pathway from the cortex to the hypothalamus (such as was described by one of us [F. A. M.[4]] as existing in the ape), an intermediate pathway (such as was described by Beattie, Brow and Long [5] and Krieg [6]) and a terminal autonomic path.

From our observations it would further appear that ulceration is only one phase of a much more extensive disturbance of the gastro-intestinal tract due to autonomic imbalance. We have recently obtained evidence (in one dog) of a postoperative increase in hydrochloric acid in the gastric juice and also of stasis. It is interesting to speculate on the possible reaction of this stasis to the classic thrombotic central artery of a gastric ulcer.

SUMMARY

Localized lesion of the frontal cortex of the cat produces a train of events which involves increased activity of the gastro-intestinal tract, at first with increased and later with decreased pyloric tonus. The tone of the cardia, the rate of propagation of the gastric waves, the number of gastric waves present and the number of waves passing in the stomach per minute are also affected. The relaxation of pyloric tone is accompanied by anorexia and succeeded by marasmus and death. Ulcer-like erosions of the gastric mucosa are noted at autopsy in animals with

2. Watts, J. W.: The Influence of the Cerebral Cortex on Gastro-Intestinal Movements, J. A. M. A. **104**:355 (Feb. 2) 1935.

3. Watts, J. W., and Fulton, J. F.: New England J. Med. **210**:883, 1934.

4. Mettler, Fred A.: J. Comp. Neurol. **61**:509, 1935.

5. Beattie, J.; Brow, G. R., and Long, C. N. H.: Proc. Roy. Soc., London, s. B **106**:253, 1930.

6. Krieg, W. J. S.: J. Comp. Neurol. **55**:19, 1932.

long-standing injury, and hyperemia and congestion are to be expected in animals with more recent damage.

PROTOCOLS

A brief résumé of the various procedures carried out on each animal is given in the following tabulation:

Operation No.	Animal No	Operation
2	4	Bilateral removal of the occipital lobe and partial removal of the parietal lobe
3	7	Removal of the left frontal lobe
4	5	Bilateral lesion of the frontal lobe
5	6	Removal of the left parietal, occipital and temporal lobes
	3	None
7	7	Removal of the right frontal lobe
8	6	Removal of the left frontal lobe

ANIMAL 3 (female).—An operation was not performed (observations do not appear in figure 1). The animal was kept under conditions identical with those of the other laboratory animals and was repeatedly subjected to feedings of a barium meal and to fluoroscopic examination. There was no deviation from normal variations.

ANIMAL 4 (male; bilateral removal of the occipital lobe and partial removal of the parietal lobe [fig. 1, no. 2]).—Slight deviation from normal variations occurred shortly after the operation. There was a transitory loss of appetite on the fifteenth day. The animal died about two months after the operation of an unknown cause. The stomach showed some hyperemia in the dependent portion.

ANIMAL 5 (male; bilateral ablation of the frontal pole [fig. 1, no. 4]).—This animal early showed intestinal overactivity and shortly afterward gave evidence of hypertonus of the pyloric sphincter. Nineteen days after the operation anorexia appeared (forced feeding then being instituted) and was succeeded by pyloric relaxation and relaxation of the cardia. The animal was killed on the twenty-fourth day. The stomach showed ulcer-like erosions.

ANIMAL 6 (female; two operations: ablation of the left occipital, parietal and temporal lobes [fig. 1, no. 5] and, seven days later, removal of the left frontal lobe [fig. 1, no. 8]).—Early after the first operation intestinal and pyloric overactivity manifested themselves. At the beginning of the fourth postoperative day, however, no deviation from normal was apparent. Following the second operation the intestinal and pyloric overactivity continued for ten postoperative days. Anorexia appeared on the seventh day, and forced feeding was instituted. Relaxation of the cardia appeared on the eighth day and pyloric relaxation on the tenth, and the animal died on the eleventh day. At autopsy the stomach was red and hemorrhagic and presented small ulcerated areas.

ANIMAL 7 (female; two operations: ablation of the left frontal lobe [fig. 1, no 3] and, seven days later, removal of the right frontal lobe [fig. 1, no. 7]).—Early after the first operation and during the first two postoperative days intestinal overactivity was observed. No further observations were made on this point, and, no other deviations being observed, the animal was again operated on seven days later. Following the second operation the animal would not eat spontaneously, and relaxation of the cardia was observed during the first postoperative day. Pyloric overactivity was present at the end of the first day, and at the end of the third day pyloric relaxation occurred. The animal died on the fourth postoperative day. The stomach was hyperemic and was ulcerated near the cardia. The antrum was apparently normal. The duodenum showed numerous small hyperemic spots.

ACHOLIC CACHEXIA

EXPERIMENTAL STUDIES

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Acholic cachexia, or cachexia cholipriva, is a condition of rapid emaciation terminating fatally which results from complete external drainage of bile. It is indeed astonishing that the prompt fatal outcome of this condition has been recognized only in recent years. Wangensteen's [1] recent review of the older literature revealed a truly astonishing series of statements made by many of the foremost scholars of the last two generations and continuing up to the early 1920's. Such able clinicians as Moynihan,[2] Murphy,[3] Courvoisier,[4] Robson,[5] Deaver [6] and Balfour and Ross [7] published comments on the apparent innocuousness of complete loss of bile. All believed it was harmless, although Balfour commented on anemia which usually appeared. Bernays,[8] on clinical evidence, stated that "bile is almost if not entirely as much of a secretion as urine."

However, since the decisive series of studies by Whipple and his co-workers, the true conditions have been more clearly understood. One

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From the Department of Surgery, the University of Chicago.

This work was done under a grant from the Jesse Horton Koessler Fund of the Institute of Medicine.

1. Wangensteen, O. H.: Complete External Biliary Fistula: Potential Serious Postoperative Complications, J. A. M. A. **93**:1199 (Oct. 19) 1929.

2. Moynihan, Berkley: Essays on Surgical Subjects: Acute Emergencies of Abdominal Disease, Philadelphia, W. B. Saunders Company, 1921, p. 144.

3. Murphy, J. B., quoted by Ferguson, A. H.: Chicago M. Rec. **9**:155, 1895.

4. Courvoisier, L. G.: Casuistisch-statistische Beiträge zur Pathologie und Chirurgie der Gallenwege, Leipzig, F. C. W. Vogel, 1890, vol. 12, p. 293.

5. Robson, A. W. M.: Observations on the Secretion of Bile in a Case of Biliary Fistula, Proc. Roy. Soc. London **47**:499, 1890.

6. Deaver, J. B., in discussion on Heyd, C. G.: Cholecystogastrostomy and Courvoisier Gallbladder, J. A. M. A. **77**: 339 (July 30) 1921.

7. Balfour, D. C., and Ross, J. W.: Postoperative Biliary Fistulas, Arch. Surg. **3**:582 (Nov.) 1921.

8. Bernays, A. C.: A Successful Case of Ideal Cholecystotomy, with Critical Remarks on the Pathology and the Different Operative Procedures Practiced on the System of Gall Vessels, Weekly M. Rev., Chicago **12**:350, 1885.

of their many significant contributions was the establishment of the fact that although complete external biliary drainage was invariably rapidly fatal, it took but minimum amounts of bile, administered by mouth or leaking into the intestine through an incompletely occluded choledochus, to maintain animals in perfect health for many years.[9] This amount for the dog is distinctly under 5 cc. per day per kilogram of body weight. In man it has never been accurately determined but is probably of the same order of magnitude.

With these points in view one can evaluate more clearly the exceedingly contradictory evidence both from the clinic and from the experimental laboratory. From a clinical standpoint, one can see at once that most of the biliary fistulas which were studied originated in stones and strictures of the ducts and hence were, as all clinicians well know, incomplete. In the earlier days of surgery cholecystostomy was a common operation. Quite naturally in cases in which the patency of the common duct was not assured at the operation, permanent fistulas resulted, but that many of these were complete and not partial or even intermittent seems doubtful from the present knowledge. On the other hand, it is quite well known to surgeons today that disastrous results follow the establishment of an external biliary fistula in cases of obstruction of the common duct due to carcinoma. Formerly this was frequently done with intent to relieve the jaundice, or, as I have heard it expressed, "to let the poisonous bile out of the system." Today even the student of medicine knows that with such external drainage of bile the patient, already emaciated from starvation and cancerous cachexia, seldom survives for even a month. Substituting a complete external biliary fistula in a case of jaundice in order to relieve toxemia has no scientific basis. To our knowledge the dogs which survived the longest with complete fistulas are the two 5½ months old which are reported on in this paper. On the other hand, Dostal and Andrews[10] maintained a dog alive for sixteen months with complete jaundice. Most dogs with complete biliary fistulas live less than two months, while most with complete jaundice survive for about six. McWhorter,[11] in some studies on choledochus cysts, called attention to the fact that intermittent and severe jaundice, which is associated with them, is not incompatible with long survival, while all patients, twenty-two in number, in whose cases external drainage was done died.

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9. Queen, F. B.; Hawkins, W. B., and Whipple, G. H.: Splenectomy in Bile Fistula Dogs, J. Exper. Med. **57**:399, 1933.

10. Dostal, L. E., and Andrews, E.: Sixteen Months' Survival with Complete Biliary Obstruction in a Dog, Proc. Soc. Exper. Biol. & Med. **29**:547, 1929.

11. McWhorter, G. L.: Congenital Cystic Dilatation of the Common Bile Duct, Arch. Surg. **8**:604 (March) 1924.

In the experimental laboratory, the results of establishing external drainage of bile apparently have always been conflicting to a surprising degree. Beginning with Schwann [12] and Bidder and Schmidt [13] nearly one hundred years ago, the operation has usually given a fatal outcome in from two to three months, and it is unnecessary to do more than mention the fact that a bibliography running into hundreds of items might be built up on this subject. On the other hand, in 1882 Röhmann [14] was able to keep such experimental animals in good health for long periods and, backed by rapidly increasing experience with clinical patients, the view that a fatal outcome was sure and that lack of bile in the system was per se a cause of cachexia never seemed to be firmly established.

The reasons for this confusion may be summed up as follows. They have to do mostly with unexpected and unforeseeable technical points in experimental technic:

1. A fistula that leaks bile on the dog's abdominal wall is worthless, as the animals may lick the fistula and thus get sufficient bile to thrive for an indefinite period. Bile, even its own, is apparently quite a delicacy to the carnivorous animal. It is probably the most highly seasoned dish the animal ever encounters. The tendency of the carnivorous animal to eat the liver of its prey first is well known. Even man may acquire a craving for his own bile.[15] Many such cases have been reported, although more often the repulsion is great.

2. The thin-walled choledochus in the laboratory animal has an uncanny power of allowing a ligature to slough through while completely reestablishing its lumen. In the clinic we had long known that veins have such potentialities, but that it is also true in the common duct of the dog was surprising. We have repeatedly seen this happen in a few weeks following operation and, on opening the animals, have found to our astonishment that it was even difficult to tell where the ligature had been placed. It is necessary, therefore, to ligate the duct doubly with silk (not catgut) ligatures and to excise a considerable piece of it.

3. There are frequently abnormal ducts in animals. These tend to lie near the main duct, but at times they are at a considerable distance. It is common in experiments to find that such ducts (which originally must have been almost capillary in size, since for a long period the stools remain free from bile) slowly hypertrophy until a normal bile flow is reestablished. This happens in experiments both in the case of jaundice and in the case of fistulas. Among ten dogs in the series reported on here in which an attempt was made to prolong survival, four had to be discarded after three months for this reason.

4. In long continued experiments with the biliary fistula ascending infection of the bile passage, with resulting hepatitis or degenerative changes in the liver, is a complication the avoidance of which is exceedingly difficult. As will be shown in

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12. Schwann, T. H.: Versuche um Auszumitteln ob die Galle im Organismus eine für das Leben wesentliche Rolle spielt, Arch. f. Anat. u. Physiol., 1884, p. 127.

13. Bidder and Schmidt, quoted by Röhmann.[14]

14. Röhmann, F.: Beobachtungen an Hunden mit Gallenfistel, Arch. f. d. ges. Physiol. **29**:509, 1882.

15. Ross, S. G.: A Study of Bile Secretion from a Case of Biliary Fistula, J. Lab. & Clin. Med. **12**:1067, 1927.

our results, we have reason to believe that many of the previously reported phenomena usually associated with acholic cachexia are more readily explicable as manifestations of damage to the liver.

METHODS

It is quite clear, therefore, that the type of experimental preparation used is an important, if not the most important, factor in the study of biliary cachexia. For these reasons it is necessary to review the various experimental set-ups used and to comment on their relative value in experiments planned for various purposes. The objects to be sought are: to avoid ascending infection, to prevent damage to the liver and to provide for collection of bile. The simple cholecystostomy with ligation of the common duct has many drawbacks. The gallbladder of the dog is not sufficiently long to reach the skin, and therefore complete epithelialization of the tract is impossible. It usually pulls away, and the gap becomes a tract lined by granulation tissue which not only contaminates the bile for analysis but causes infection. Collection of all the bile from such a fistula soon becomes impossible, and leakage about a tube in the gallbladder usually occurs. The odor and taste of this soon stirs up the dog to attempt to lick or eat his own bile, thus defeating the purpose of the experiment. A plaster collar to prevent the dog's reaching the fistula is only partially successful.

Furthermore, in this type of fistula the gallbladder tends to retract from the skin, and the resulting sinus, although it may be kept patent by the pressure of the bile, becomes very narrow. The result is that the gallbladder remains full of bile and overflows only under pressure. Thus the bile is constantly subjected to the concentrating action of the mucosa of the gallbladder and in composition resembles bile from the bladder much more than bile from the liver.

The insertion of a tube into the common duct with or without accompanying cholecystectomy is a marked advance. Even with this method ascending infection is common, and in our experience there has always been the great drawback that after weeks or months the cannula is very likely to slip out. In experiments intended to last until death from acholic cachexia takes place such a set-up usually results in disappointment at a critical time—the rapid terminal collapse of the animal. In 1923 Rous and McMaster[16] reported a method which seemed to overcome many of these difficulties. They avoided ascending infection from the outside by using a much longer tube than was necessary simply to reach the skin, the extra coils of which were allowed to lie within the abdomen. Thus the liver was placed at a much greater distance from the skin, and hepatitis did not take place. Furthermore the long coils did not favor the pulling out of the tube from its insertion into the duct by accidental trauma. While some workers[17] found that this type of fistula gives very good results, others encountered great technical difficulties.[18] In our experience the preparation usually did not last long enough to enable us to follow a dog through until death. After a few weeks the tubes tended to become clogged with deposits of pigment and calcium, and periods of jaundice

16. Rous, P., and McMaster, P. D.: A Method for Permanent Sterile Drainage of Intra-Abdominal Ducts as Applied to a Common Duct, J. Exper. Med. **37**: 11, 1923.

17. Elman, R., and Hartmann, H. F.: Spontaneous Peptic Ulcers of Duodenum After Continued Loss of Total Pancreatic Juice, Arch. Surg. **23**:1030 (Dec.) 1931.

18. Dostal, L. E., and Andrews, E.: Etiology of Gallstones: III. Effect of Diet on Bile Salt-Cholesterol Ratio, Arch. Surg. **26**:258 (Feb.) 1933.

occurred. Infection of the liver was often not prevented but simply delayed. It makes an ideal method of collecting bile for short periods, especially when a two-way fistula is made and the bile returned to the duodenum when desired.

Cholecystnephrostomy, as reported by Kapsinow, Engle and Harvey in 1924,[19] offers many advantages. The gallbladder is dissected free from the liver and after being opened is implanted into the right renal pelvis through an opening in the parenchyma. The bile is then easily collected with the urine in a metabolism cage. The drawback to this method is that complete epitheliation of the tract does not take place and consequently granulating surfaces may persist, as evidenced by pus in the mixed bile and urine. While for many purposes such a set-up is ideal, in our hands there was usually profound damage to the liver, and consequently none of our animals in which this was done lived as long as those with simple cannulas often do.

More recently Puestow[20] transplanted the section of the duodenum containing the ampulla of Vater on the anterior abdominal wall, with or without cholecystectomy. This procedure gives an ideal method of studying the flow of bile under various conditions, and the dogs can be kept alive for indefinite periods if allowed to lick the fistulas. For experiments of short duration this method is of great value, but for long ones it is very difficult to collect all the bile and the tendency to lick the fistulas is very great.

The apparatus recently devised by Dragstedt and his co-workers[21] for the making of a pancreatic fistula was applied to the gallbladder with singular success. The cannula is gold-plated metal with a small flange on the inner end to prevent its slipping out of the gallbladder and on the outer end a threaded tip. On this was screwed a sharp spear so that it could be thrust through the abdominal wall, thus assuring a tight fit and preventing the necessity of bringing it out through the operative wound. The spear tip was then unscrewed and (fig. 1) a metal extension screwed on, to which could be attached a football bladder for collection. For use in the gallbladder this was modified slightly, making it longer to permit the necessary access to the dog's rather deeply placed gallbladder and allowing for the ample respiratory excursion of this viscus in the dog. The part intervening between the edge of the gallbladder and the abdominal wall was wrapped in omentum. The inner flanged end was inserted into the gallbladder through as small a hole as possible without inverting the edges and simply tied in place. This apparatus has the disadvantage of not entirely doing away with the action of the gallbladder in concentrating the bile, but as the opening is large and gravity favors rapid drainage, it is evident that the bile never remains in the gallbladder for a very long period. This point may be confirmed by reference to the tables, in which it can be seen at once that the analysis showed that the bile was from the liver and did not partake of the character of that from the bladder. It is true, however, that the secretion of the gallbladder is mixed with the bile, even if the bile does not stay in the viscus long enough to undergo any significant concentration. Our success with this type of fistula has been gratifying. It has been used in over thirty dogs. Nearly 1,500 specimens of bile have been thus

19. Kapsinow, R.; Engle, L. P., and Harvey, S. C.: Intra-Abdominal Biliary Exclusion from the Intestines: Cholecysto-Nephrostomy, a New Method, Surg., Gynec. & Obst. **39**:65, 1924.

20. Puestow, C. B.: The Discharge of Bile into the Duodenum, Arch. Surg. **23**:1013 (Dec.) 1931.

21. Dragstedt, L. R.; Haymond, H. E., and Ellis, J. C.: Cannula Gastrostomy and Enterostomy, Surg., Gynec. & Obst. **56**:799, 1933.

collected, and the number of lost specimens is under 1 per cent. In a few cases there was deposit of biliary concretions on the tube to such an extent as to obstruct it partially, but with the knowledge of exactly how long the tube was, it was a very simple matter to insert a probe and scrape this deposit out without damaging the gallbladder. When obstructed, a few drops of bile may appear about the tube, or the appearance of slight jaundice gives warning. The football bladder is slung about the dog's abdomen in a linen bag. The fistula is almost invariably completely dry, and no bile leaks about the outside of the tube. It is perhaps for this reason that we did not find it necessary to put plaster collars on the dogs, as when there is no bile on the skin the tendency to lick or bite the apparatus does not seem to be present.

With the use of this preparation we kept four dogs alive for from four and one-half to five and one-half months, considerably longer than the usual period of survival when other types of fistula are used. The absence of ascending infection in all cases was striking, and the liver did not show the usual damage found in animals with experimental biliary fistulas. As will be seen, this prob-

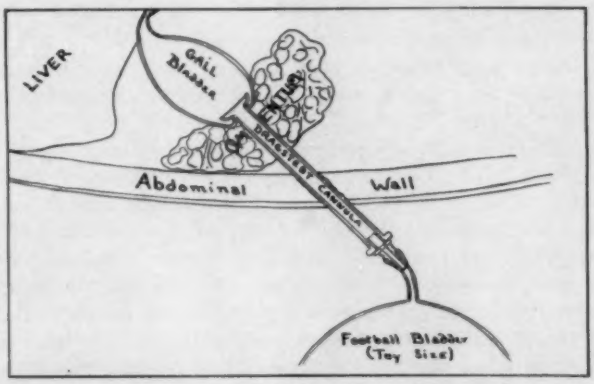

Fig. 1.—Diagram showing the use of the Dragstedt cannula in the deeply placed gallbladder of the dog. The part intervening between the edge of the gallbladder and the abdominal wall is wrapped in omentum.

ably accounts for the fact that many of the phenomena usually said to be the results of acholic cachexia were not found in our animals.

All these various types of preparations have been used, for the most part in experiments of short duration. In all those designed to last for periods of more than from two to three weeks, the Dragstedt cannula was used. The protocols as well as the results of the various groups of experiments and the comment will be given under separate headings. However, since over one-half of our data were taken from the results obtained on four dogs in which intensive studies were made for very long periods, the protocols of these will be given in detail first. The four large tables are illustrative of these experiments and are included for cross-reference, although for the sake of clarity data from them are sometimes included with other material in smaller tables.

PROTOCOLS

Cholecystostomy was performed on dogs under ether anesthesia and the Dragstedt cannula inserted according to the method just described. Primary union

was attained in all dogs reported on. Feedings were begun the day after operation, but usually all the food offered was not consumed until seven or eight days after operation. During the rest of the periods of observation all the food was immediately and avidly consumed.

The diet consisted of 250 Gm. of lean meat and 200 Gm. of bread. The meat was cooked and then ground with the bread into a homogeneous paste, with the addition of about 500 cc. of water per ration. Drinking water was supplied ad libitum. One day a week the dogs were given only water. Aliquot samples of each batch of meat were taken for determination of cholesterol. It was found that the cholesterol content of the bread was constant, and therefore each loaf was not tested. The portions were weighed each day in order that the total weight of the food consumed might be calculated and, from this, the cholesterol content in the diet. On this diet the stools were generally formed. As seen in tables 1 to 4, the dogs were put on a diet of raw meat in the latter portion of the period of their survival. Under this regimen attacks of diarrhea occurred, and to control this complication bone ash was occasionally added to the diet.

For the various analyses samples of blood, 30 cc. each, were needed, and about twenty were taken over periods of from four to five months—not an insignificant total quantity in relation to the onset of anemia. In the early stages such samples were taken every four days, but later these periods were lengthened to eight days and then to sixteen days, or even longer. Determinations of blood cholesterol were made by the original Bloor method.[22] Tests for fragility were made by the Sanford [23] method; for blood fats by the Bloor [24] method, and for free and bound calcium by Clark and Collip's [25] modification of the Kramer and Tisdall method.[26] The red blood cell counts were made with an ordinary pipet and the hemoglobin estimations by the Sahli scale.

The bile was collected from the bags daily. It was found unnecessary to use precaution to insure sterility. The specimens were put into 2 volumes of alcohol for preservation and pooled for analysis for periods, as shown in the tables. In each instance the football bladder was washed daily, as was the canvas bag in which it was slung about the dog's abdomen. The bile was measured daily and the analysis for bile salts and cholesterol made by a method previously reported by Andrews and Hrdina.[27] The acid content of the bile was estimated by the aminonitrogen method of Schmidt and Dart [28] and expressed as glycocholic acid.

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TABLE 1.—*Data on Dog 940 with an Experimental Biliary Fistula*

Date	Body Weight, Kg.	Blood							Bile									Feces			Food				Comment
		Red Blood Corpuscles per Cu. Mm.	Hemoglobin, per Cent	Fragility		Fats, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Calcium, Mg. per 100 Cc.	Total Output, Cc.	Daily Output, Cc.	Daily Output per Kilogram, Cc.	Cholesterol			Bile Acids				Dry Weight, Gm.	Cholesterol, Mg. per 100 Cc.	Total Cholesterol, Mg.	Meat		Bread		
												Mg. per 100 Cc.	Average Daily Output, Mg.	Total Output, Mg.	Mg. per 100 Cc.	Average Daily Output, Mg.	Total Output, Mg.	Output per Kg. per Day, Mg.	Bile Acids-Cholesterol Ratio				Weight, Gm.	Total Cholesterol, Mg.	Weight, Gm.	Total Cholesterol, Mg.	
					Fragility																				
4/28/33	18.4	6,540,000	80	0.46	0.36	107	213.5	11.16	.....	.....	.....	.....	.....	.....	.....	.....	.....	..	..	...	...	...	.....	.....	.....	.....	Normal
5/ 2/33	18.5	6,760,000	78	0.44	0.30	115	207	12.1	.....	.....	.....	.....	.....	.....	.....	.....	.....	..	..	...	...	...	.....	.....	.....	.....	Normal
5/ 3/33	....	.....	..	....	....	...	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	..	..	...	...	...	.....	.....	.....	.....	Operation
5/ 6/33	19	6,240,000	75	0.44	0.36	158	240	11.7	.....	.....	.....	.....	.....	.....	.....	.....	.....	..	..	...	...	...	.....	.....	.....	.....	
5/11/33	18.5	5,100,000	75	0.50	0.36	130	180	11.5	1,202	133	7.3	13.3	17	137.8	654	1,308	7,861	48	49	143	115	164	538	995	261	391	
5/15/33	17.4	6,040,000	70	0.48	0.34	120	204	11.9	.....	.....	.....	.....	.....	.....	.....	.....	.....	..	..	...	...	...	946	1,453	757	1,892	
5/19/33	17	4,810,000	70	0.40	0.34	99	168	12.4	1,560	195	11.4	8	15.2	237	292	554	4,545	43	36	103	150	154	736	1,770	488	1,220	(1) Serum jaundiced; (2) tetanic convulsions for 15 min.; (3) corneal opacity of eye (left)
5/23/33	16.8	4,520,000	60	0.44	0.34	100	170.4	11.3	878	219	13	10	22	87.8	308	665	2,660	39	30	32	115	36	912	1,963	730	1,820	Serum jaundiced
5/27/33	15.6	3,920,000	62	0.44	0.40	130	213.5	13	948	237	15	4.1	9.7	38.8	386	914.8	3,658	58	94	80	105	84	720	1,565	576	1,440	Eyes normal; serum jaundiced
6/ 1/33	15	6,560,000	68	0.44	0.34	111	194	11.7	1,234	308	20.5	6.3	15.5	72.5	501	1,237	6,182	102	79	53.5	120	64	922	2,195	748	1,870	
6/ 5/33	16.5	6,710,000	64	0.44	0.34	107	176.4	11.2	1,042	200	12	9.1	23.7	94.8	529	1,375	5,512	63	58	87	150	130	968	953	774	1,935	
6/ 9/33	16.8	4,760,000	78	0.44	0.28	143	176.4	12.1	1,021	255	15	12	30.6	122.5	446	1,137	4,553	67	37	58	184	106	750	2,000	600	1,500	
6/13/33	16.2	5,480,000	75	0.46	0.30	111	150	11.3	1,062	265	16	24	63.7	254.8	244	646	2,691	39	10	157	100	157	1,000	2,000	800	1,080	
6/21/33	16	6,950,000	75	0.46	0.32	99	150	11.7	2,252	281	17.8	2.2	6.19	49.5	430	1,208	9,783	76	195	143	79	112	750	1,000	600	810	
6/29/33	15.4	6,300,000	70	0.44	0.32	84	150	9.9	2,270	283	18	3	8.51	68.1	386	1,095	8,762	69	44	120	142	170	1,750	2,055	1,400	1,890	
7/ 7/33	15.2	.....	65	0.46	0.34	130	142.8	9.8	2,270	283	18	5.3	15	114.3	349	976	7,922	63	21	239	165	394	1,750	3,536	1,400	1,890	
7/24/33	14.8	6,890,000	75	0.46	0.30	123	162	10	4,835	284	19	3.2	9.1	154.7	98	278	3,938	19	30	65	135	87	1,750	2,546	1,400	1,890	
8/ 1/33	14.4	5,970,000	65	0.44	0.34	107	158	9.9	2,728	341	23.5	2.3	6.9	62.7	198	675	5,401	46	86	120	110	132	3,500	3,512	2,800	3,780	
8/25/33	13.2	.....	..	....	....	...	.....	.....	4,103	164	12.3	12.6	36.2	516.9	36	61.5	1,477	44	3	...	...	...	8,000	2,424	6,000	7,100	
Totals									27,347	3,448	218.8	115.4	279.3	2,012.2	4,852	12,130.3	74,945	776	723			1,790	29,967			30,508	Dog killed
Averages									235.7		15.6	8.2	19.2		346	566.4		55.4									

TABLE 2.—*Data on Dog 958 with an Experimental Biliary Fistula*

Date	Body Weight, Kg.	Blood							Bile										Feces			Food				Comment
		Red Blood Corpuscles per Cu. Mm.	Hemoglobin, per Cent	Fragility		Fats, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Calcium, Mg. per 100 Cc.	Total Output, Cc.	Daily Output, Cc.	Daily Output per Kilogram, Cc.	Cholesterol			Bile Acids				Dry Weight, Gm.	Cholesterol, Mg. per 100 Cc.	Total Cholesterol, Mg.	Meat		Bread		
												Mg. per 100 Cc.	Average Daily Output, Mg.	Total Output, Mg.	Mg. per 100 Cc.	Average Daily Output, Mg.	Total Output, Mg.	Output per Kg. per Day, Mg.	Bile Acids-Cholesterol Ratio				Weight, Gm.	Total Cholesterol, Mg.	Weight, Gm.	Total Cholesterol, Mg.	
4/20/33	19.5	6,880,000	74	0.38	0.30	107	176.4	12.1	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	.....	.....	.....	.....	.....	Normal blood
4/24/33	19.5	6,650,000	75	0.40	0.42	111	200	11.1	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	.....	.....	.....	.....	.....	Normal blood
4/28/33	18	5,530,000	76	0.38	....	150	195	10.8	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	.....	335	881	187	280	Operation, 4/25/33
5/ 2/33	18	5,200,000	76	0.38	....	166	200	10.5	388	48	2.8	8.2	3.7	31.8	529	355	2,052	15	64	110	215	236.5	539	610	453	679	Slight jaundice
5/ 6/33	18	4,990,000	70	0.38	0.30	130	130	11.5	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	.....	531	1,283	431	646	Serum jaundice
5/11/33	18	5,250,000	60	0.50	0.34	111	136	11.1	578	64	3.5	8.0	5.0	46.24	503	272.4	2,907	18	63	124	130	161.2	983	1,702	786	1,179	
5/15/33	17.5	5,600,000	62	0.42	0.30	130	138.8	12.5	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	.....	723	1,807	578	867	
5/19/33	17.5	4,570,000	60	0.42	0.38	130	166	12.5	694	86	4.9	12.0	10.0	83.28	463	357	3,213	23	38	50	187	93.5	990	2,165	792	1,188	
5/23/33	17.4	4,300,000	58	0.46	0.36	115	142.8	11.7	200	50	3	13.0	6.5	26.0	369	180	738	11	28	...	...	.....	728	1,577	582	873	
5/27/33	17.6	4,060,000	73	0.42	0.38	115	144	11.0	412	103	5.8	13.3	13.6	46.0	595	612.8	2,451	34	44	67	100	67	848	1,826	678	1,017	
6/ 1/33	18	4,530,000	60	0.44	0.32	120	120	11.3	565	141	7.9	9.4	13.2	53.11	535	503	2,841	43	57	108	165	178.2	730	967	584	876	
6/ 5/33	18	4,860,000	70	0.44	0.34	107	154.8	11.7	470	117	6.5	33.3	39	15.65	521	612	2,448	34	15	55	173	95.1	750	2,000	600	900	
6/ 9/33	18	5,140,000	70	0.44	0.36	150	136	11.7	414	103	5.7	10.9	11.2	45.1	372	385	1,540	21	34	70	85	59.5	1,000	1,500	800	1,080	
6/13/33	17.6	5,390,000	65	0.44	0.32	109	158	10.7	404	101	5.7	6.6	6.6	26.66	414	418	1,672	14	62	142	80	113.6	750	1,500	600	810	
6/21/33	17.4	4,930,000	70	0.46	0.34	107	150	10.4	1,032	129	7.4	15.0	19	15.48	389	502	4,014	29	26	123	135	166	1,750	2,040	1,400	1,890	
6/29/33	17.4	5,260,000	70	0.42	0.32	93.7	130.4	9.9	1,084	129	7.4	6.0	7.7	62.0	450	517	4,653	33	75	95	90	85.5	1,750	3,238	1,400	1,890	
7/ 7/33	17	.....	70	0.44	0.32	136	130.4	9.7	1,038	129	7.5	6.0	7.7	62.0	357	463	3,705	27	59	190	115	218.5	1,750	2,437	1,400	1,890	
7/24/33	16	6,110,000	75	0.44	0.30	136	150.0	9.7	2,096	123	7.6	5.5	6.2	11.5	439	524	9,201	33	80	198	105	207.9	3,500	3,130	2,800	2,780	
8/ 9/33	15.4	5,560,000	65	0.44	0.32	117	166.0	9.9	2,274	132	8.5	8.8	11.6	20.0	412	585	9,368	35	46	107	215	230	1,750	4,685	1,400	1,890	
8/28/33	14.4	5,220,000	60	0.44	0.34	93.7	213.5	10.0	519	30	2.0	20.0	6	103.8	389	201	2,018	8	19	...	...	.....	5,000	6,173	2,400	3,240	Began feeding; 500 Gm. meat, 8/24/32
9/ 1/33	....	.....	..	....	....	...	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	...	.....	.....	.....	.....	Daily subcutaneous injection of 0.5 cc. of viosterol was begun 9/1/33
9/14/33	12.2	4,670,000	68	0.44	0.36	130	158	9.7	1,782	104	8.5	12	12.4	21.3	387	444	6,896	33	32	15	104	15.6	7,500	.....	.....	.....	
9/28/33	11.0	4,170,000	54	0.42	0.34	130	230	9.7	1,466	112	10	15	16.8	22.0	585	587	8,576	58	39	...	...	.....	5,000	.....	.....	.....	
Totals									15,366	2,423	104.3	208	196.2	691.9	7,709	7,511	68,293	469	781			1,927.1		39,521		21,644	Dog killed
Averages									99		6.1	12	11.5		453	441		27.5								

TABLE 3.—*Data on Dog [illegible] with an Experimental Biliary Fistula*

Date	Body Weight, Kg.	Blood							Bile										Feces			Food				Comment
		Red Blood Corpuscles per Cu. Mm.	Hemoglobin, per Cent	Fragility		Fats, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Calcium, Mg. per 100 Cc.	Total Output, Cc.	Daily Output, Cc.	Daily Output per Kilogram, Cc.	Cholesterol			Bile Acids				Dry Weight, Gm.	Cholesterol, Mg. per 100 Cc.	Total Cholesterol, Mg.	Meat		Bread		
												Mg. per 100 Cc.	Average Daily Output, Mg.	Total Output, Mg.	Mg. per 100 Cc.	Average Daily Output, Mg.	Total Output, Mg.	Output per Kg. per Day, Mg.	Bile Acids-Cholesterol Ratio				Weight, Gm.	Total Cholesterol, Mg.	Weight, Gm.	Total Cholesterol, Mg.	
4/ 1/33	18.5	6,000,000	70	0.38	0.30	107	176.4	12.1	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	.....	.....	.....	.....	.....	Normal blood
4/ 5/33	18.5	6,650,000	75	0.40	0.42	111	200	11.1	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	.....	.....	.....	.....	.....	Normal blood
4/ 9/33	18	5,530,000	76	0.38	....	150	195	10.8	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	.....	335	881	187	280	Operation, 4/6/33
4/13/33	18	5,200,000	76	0.38	....	166	200	10.5	388	48	2.8	8.2	3.7	31.8	529	355	2,052	15	64	110	215	236.5	539	610	453	679	Slight jaundice
4/17/33	18	4,990,000	70	0.38	0.30	130	130	11.5	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	.....	531	1,283	431	646	Serum jaundice
4/22/33	18	5,250,000	60	0.50	0.34	111	136	11.1	578	64	3.5	8.0	5.0	46.24	503	272.4	2,907	18	63	124	130	161.2	983	1,702	786	1,179	
4/26/33	17.5	5,600,000	62	0.42	0.30	130	138.8	12.5	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	.....	723	1,807	578	867	
4/30/33	17.5	4,570,000	60	0.42	0.38	130	166	12.5	694	86	4.9	12.0	10.0	83.28	463	357	3,213	23	38	50	187	93.5	990	2,165	792	1,188	
5/ 4/33	17.4	4,300,000	58	0.46	0.36	115	142.8	11.7	200	50	3	13.0	6.5	26.0	369	180	738	11	28	...	...	.....	728	1,577	582	873	
5/ 8/33	17.6	4,060,000	73	0.42	0.38	115	144	11.0	412	103	5.8	13.3	13.6	46.0	595	612.8	2,451	34	44	67	100	67	848	1,826	678	1,017	
5/12/33	18	4,530,000	60	0.44	0.32	120	120	11.3	565	141	7.9	9.4	13.2	53.11	535	503	2,841	43	57	108	165	178.2	730	967	584	876	
5/16/33	18	4,860,000	70	0.44	0.34	107	154.8	11.7	470	117	6.5	33.3	39	15.65	521	612	2,448	34	15	55	173	95.1	750	2,000	600	900	
5/20/33	18	5,140,000	70	0.44	0.36	150	136	11.7	414	103	5.7	10.9	11.2	45.1	372	385	1,540	21	34	70	85	59.5	1,000	1,500	800	1,080	
5/24/33	17.6	5,390,000	65	0.44	0.32	109	158	10.7	404	101	5.7	6.6	6.6	26.66	414	418	1,672	14	62	142	80	113.6	750	1,500	600	810	
6/ 1/33	17.4	4,930,000	70	0.46	0.34	107	150	10.4	1,032	129	7.4	15.0	19	15.48	389	502	4,014	29	26	123	135	166	1,750	2,040	1,400	1,890	
6/ 9/33	17.4	5,260,000	70	0.42	0.32	93.7	130.4	9.9	1,084	129	7.4	6.0	7.7	62.0	450	517	4,653	33	75	95	90	85.5	1,750	3,238	1,400	1,890	
6/17/33	17	.....	70	0.44	0.32	136	130.4	9.7	1,038	129	7.5	6.0	7.7	62.0	357	463	3,705	27	59	190	115	218.5	1,750	2,437	1,400	1,890	
6/25/33	16	6,110,000	75	0.44	0.30	136	150.0	9.7	2,096	123	7.6	5.5	6.2	11.5	439	524	9,201	33	80	198	105	207.9	3,500	3,130	2,800	2,780	
7/ 3/33	15.4	5,560,000	65	0.44	0.32	117	166.0	9.9	2,274	132	8.5	8.8	11.6	20.0	412	585	9,368	35	46	107	215	230	1,750	4,685	1,400	1,890	
7/22/33	14.4	5,220,000	60	0.44	0.34	93.7	213.5	10.0	519	30	2.0	20.0	6	103.8	389	201	2,018	8	19	...	...	.....	5,000	6,173	2,400	3,240	Began feeding; 500 Gm. meat, 7/18/33
7/25/33	....	.....	..	....	....	...	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	...	.....	.....	.....	.....	Daily subcutaneous injection of 0.5 cc. of viosterol was begun 7/25/33
8/ 7/33	12.2	4,670,000	68	0.44	0.36	130	158	9.7	1,782	104	8.5	12	12.4	21.3	387	444	6,896	33	32	15	104	15.6	7,500	.....	.....	.....	
8/21/33	11.0	4,170,000	54	0.42	0.34	130	230	9.7	1,466	112	10	15	16.8	22.0	585	587	8,576	58	39	...	...	.....	5,000	.....	.....	.....	
Totals									15,366	2,423	104.3	208	196.2	691.9	7,709	7,511	68,293	469	781			1,927.1		39,521		21,644	Dog killed
Averages									99		6.1	12	11.5		453	441		27.5								

Averages	99		6.1	12	11.5																											

TABLE 3.—*Data on Dog 916 with an Experimental Biliary Fistula*

		Blood								Bile											Feces			Food				
													Cholesterol			Bile Acids								Meat		Bread		
Date	Body Weight, Kg.	Red Blood Corpuscles per Cu. Mm.	Hemoglobin, per Cent	Fragility		Fats, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Calcium, Mg. per 100 Cc.	Total Output, Cc.	Daily Output, Cc.	Daily Output per Kilogram, Cc.	Mg. per 100 Cc.	Average Daily Output, Mg.	Total Output, Mg.	Mg. per 100 Cc.	Average Daily Output, Mg.	Total Output, Mg.	Output per Kg. per Day, Mg.	Bile Acids-Cholesterol Ratio	Dry Weight, Gm.	Cholesterol, Mg. per 100 Cc.	Total Cholesterol, Mg.	Weight, Gm.	Total Cholesterol, Mg.	Weight, Gm.	Total Cholesterol, Mg.	Comment
4/20/33	17.5	6,460,000	75	0.36	0.32	104	277	11.8	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	...	.....	.....	.....	.....	.....	.....	Normal
4/24/33	17.4	6,500,000	76	0.42	0.32	120	213	10.5	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	...	.....	.....	.....	.....	.....	.....	Normal
5/ 2/33	17.5	5,690,000	75	0.48	0.32	86	227	11.3	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	...	.....	.....	.....	.....	.....	.....	Normal
5/ 3/33	....	.....	..	....	....	...	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	...	.....	.....	.....	.....	.....	.....	Operation
5/ 6/33	16	5,320,000	75	0.42	0.34	102	166	11.5	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	...	.....	.....	.....	718	1,450	473	709	Serum jaundiced
5/11/33	16.5	6,110,000	70	0.50	0.36	100	204	12.1	829	92	5.4	15	13	124.5	272	375	2,254.8	15	18	106	187.5	198.2	921	1,973	720	1,080	Serum normal
5/15/33	16	5,680,000	68	0.46	0.34	107	200	11.7	1,246	311	19	2.4	7.5	29.9	319	991	48.5	61	133	...	...	.....	710	1,775	568	752	
5/19/33	15.8	4,810,000	64	0.40	0.38	150	182	13.2	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	23	120	27.6	996	1,934	796	1,194	
5/23/33	15.6	5,550,000	65	0.46	0.34	125	143	11.7	618	77	4.8	24	37	148	176	135	1,087.6	8	7	53	80	42.4	715	1,549	572	758	
5/27/33	16	4,820,000	68	0.44	0.40	86	145.6	12.2	664	166	10	23.6	39	156	156	529	1,035.8	16	6	33	187.5	61.7	919	1,944	736	1,104	
6/ 1/33	16.2	5,160,000	67	0.44	0.34	115	160	11.3	766	191	11.7	15	28	114.9	188	288	1,440	22	12	40	17.3	6.9	905	966	706	1,194	
6/ 5/33	16.4	4,640,000	65	0.46	0.34	107	135	11.7	684	171	10	15	25	102.6	499	853	3,413	49	33	44	102.5	45.1	750	2,500	600	900	
6/ 9/33	16.8	4,600,000	73	0.44	0.32	115	155.4	12.1	578	119	7	24	34	136.7	404	583	2,335	28	17	40	118	47.2	1,000	2,000	800	1,080	
6/13/33	16.2	4,240,000	70	0.44	0.32	104	140	9.9	648	162	10	20	32	129.6	182	295	1,179	18	9	125	115	143.7	750	1,500	600	810	
6/21/33	16.4	4,920,000	70	0.42	0.32	90	168	10.7	1,172	146	8.9	6	9	70.3	301	441	3,527.7	27	50	87	1.15	1	1,750	2,145	1,400	1,890	
6/29/33	16.6	4,380,000	65	0.40	0.32	104	135	10.1	1,308	164	9.8	9.2	15	120.3	337	551	4,407.9	33	36	80	80	64	1,750	3,738	1,400	1,890	
7/ 7/33	16.4	.....	70	0.44	0.34	79	142.8	9.5	1,080	135	8.2	8	10	86.40	164	197	1,771.2	13	20	150	80	120	1,750	2,904	1,400	1,890	
7/24/33	16	4,680,000	65	0.44	0.30	88	130.4	10.6	3,550	206	13	2.8	5	99.4	293	609	10,401.5	38	104	112	100	112	3,500	4,669	2,800	3,780	
8/ 1/33	13.8	4,130,000	58	0.46	0.34	109	143.5	9.8	1,222	152	11	2.6	4	21.77	373	566	4,558	41	14	40	110	44	1,750	2,124	1,400	1,890	
8/ 9/33	13.6	.....	..	....	....	...	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	...	.....	1,750	2,493	1,400	1,890	
8/16/33	....	.....	..	....	....	...	.....	.....	6.8	.....	.....	.....	.....	.....	168	227	1,159	...	...	...	...	.. ..	.....	.....	.....	.....	
8/25/33	....	.....	..	....	....	...	.....	.....	755	.....	.....	.....	.....	.....	323	487	.....	...	...	...	...	.....	.....	.....	.....	.....	
8/28/33	13	4,800,000	65	0.44	0.34	120	154	9.7	.....	.....	.....	10.1	.....	.....	160	.....	.....	...	...	...	...	.....	5,250	7,745	2,200	2,970	
9/ 3/33	12.8	.....	..	....	....	...	.....	.....	213	.....	.....	16	.. ..	34	249	.....	530	...	...	...	...	.....	2,000	2,802	.....	.....	Dog killed
Totals									16,011	2,092	128.8	194	321	1,374.5	4,564	6,857	39,127.5	369	459			913.8		46,217		25,781	
Averages									142		10	12.9	24.7		268	457		28	35								

TABLE 4.—*Data on Dog 959 with an Experimental Biliary Fistula*

Date	Body Weight, Kg.	Blood							Bile										Feces			Food				Comment
												Cholesterol			Bile Acids							Meat		Bread		
		Red Blood Corpuscles per Cu. Mm.	Hemoglobin, per Cent	Fragility		Fats, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Calcium, Mg. per 100 Cc.	Total Output, Cc.	Daily Output, Cc.	Daily Output per Kilogram, Cc.	Mg. per 100 Cc.	Average Daily Output, Mg.	Total Output, Mg.	Mg. per 100 Cc.	Average Daily Output, Mg.	Total Output, Mg.	Output per Kg. per Day, Mg.	Bile Acids-Cholesterol Ratio	Dry Weight, Gm.	Cholesterol, Mg. per 100 Cc.	Total Cholesterol, Mg.	Weight, Gm.	Total Cholesterol, Mg.	Weight, Gm.	Total Cholesterol, Mg.	
4/20/33	17.5	5,820,000	76	0.42	0.32	166	258	11.5	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	...	.....	.....	.....	.....	.....	Normal
4/24/33	17.5	7,210,000	77	0.44	0.30	158	254	11.9	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	...	.....	.....	.....	.....	.....	Normal
4/25/33	....	.....	..	....	....	...	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	...	.....	.....	.....	.....	.....	Operation
4/28/33	17	7,730,000	79	0.46	0.34	150	300	11.3	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	...	.....	275	1,028	221	454	First postoperative day
5/ 2/33	16.5	6,320,000	80	0.48	0.34	150	281.5	11.1	978	108	6	4.4	4.7	43	195	238	1,936	12	44	38	300	114	693	1,960	549	823	
5/ 6/33	16.5	6,860,000	76	0.46	0.34	88	250	11.3	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	56	375	109	604	1,421	530	795	
5/11/33	16.7	6,130,000	75	0.50	0.42	115	272	12.1	914	101	6	24	24	219.3	518	676	4,734	31	21	75	165	123	970	1,777	776	1,164	
5/15/33	16.7	5,490,000	75	0.46	0.34	93.7	200	11.8	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	97	125	121	731	1,825	581	876	
5/19/33	16.8	6,170,000	75	0.46	0.38	136	250	12.3	1,384	173	10	13.3	23	184	198	293	4,055	20	14	40	150	60	993	1,875	794	1,191	
5/23/33	17	5,930,000	70	0.48	0.40	115	272	10.9	610	152	8.9	20	30	122	140	213	1,299	12	7	79	125	98	728	1,577	582	873	
5/25/33		Seven premature pups born (cholesterol estimation on litter)																									
5/27/33	16.6	3,240,000	70	0.40	0.34	115	300	11.1	526	131	7.9	40	52	210.4	344	452	7,377	27	9	34	187.5	63	883	1,800	707	1,060	Cannula occluded
6/ 1/33	16	5,160,000	64	0.46	0.40	106	215	11.4	1,223	305	19	50	152	611.5	191	467	5,711	36	4	50	100	50	977	728	782	1,173	Bile bloody for 4 days
6/ 5/33	15.4	5,720,000	65	0.44	0.36	111	190	11.7	950	237	15	48	113	456	301	714	6,783	45	6	46	150	69	750	2,000	600	900	Bile normal
6/ 9/33	15.8	4,930,000	70	0.44	0.34	104	181	11.8	692	173	10.9	40	69	276	196	339	2,345	21	5	55	187.5	103	1,000	2,000	800	1,100	Condition normal
6/13/33	15.8	4,170,000	73	0.48	0.40	120	176.4	10.8	533	133	8	60	79	321.8	159	211	847	13	3	117	102.5	119	750	1,500	600	810	
6/21/33	15.5	4,970,000	78	0.48	0.34	120	150	9.3	1,232	308	19	8.5	26	104.7	283	436	3,486	54	33	133	215	285	1,750	2,445	1,400	1,890	
6/29/33	15.4	5,780,000	77	0.48	0.32	97	142.8	10.2	1,120	140	9	23	32	257	...	366	.....	...	...	163	95	154	1,750	3,738	1,400	1,890	
7/ 7/33	15.2	.....	65	0.46	0.32	109	136	10.7	1,000	136	8.9	14.1	19	153.6	289	393	3,150	26	20	260	165	429	1,750	2,434	1,400	1,890	
7/24/33	15.6	5,600,000	70	0.46	0.32	120	250	10.4	1,615	201	13	10.9	22	176	339	322	5,474	45	31	185	115	212	3,500	4,325	2,800	3,780	
8/ 9/33	13.4	6,320,000	65	0.46	0.34	130	300	10.7	941	55	4	20.7	11	194	310	182	2,917	12	15	200	120	240	1,750	4,274	1,400	1,890	
8/25/33	12.6	5,600,000	62	0.44	0.36	107	250	9.3	1,927	120	9.5	24	28	462	.....	285	.....	...	...	...	...	.....	5,000	5,466	2,400	3,240	500 Gm. raw meat on 8/24/33
9/ 1/33	....	.....	..	....	....	...	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	...	.....	.....	.....	.....	.....	Daily subcutaneous injection of 0.5 cc. of viosterol was begun 9/1/33
9/14/33	10.4	6,200,000	68	0.42	0.36	111	198	8.5	1,347	67	6	24	16	323	290	300	3,906	17	12	90	79	23	7,500	.....	.....	.....	
9/21/33	10	.....	..	....	....	...	.....	.....	883	126	12.6	13	16	114.7	247	272	2,058	31	19	...	...	.....	3,000	.....	.....	.....	Dog killed
Totals									17,965	2,666	174	437.9	716.7	4,228.7	4,000	6,159	56,078		246			2,372		42,173		25,769	
Averages									130		10	25.7	42.1		266	362			26.8								

The feces were collected daily and pooled for periods. They were dried, powdered, mixed and weighed and aliquot samples taken. The cholesterol content was determined by the method of Bloor.[22] In most cases the period of ether-alcohol extraction was over six months. Most of the animals defecated only during their periods of exercise. When the stools were liquid, adequate collection was impossible. For this reason our figures on the cholesterol content of the stools are incomplete, probably representing less than half the actual amount passed, as it is well known that the diarrhea stool usually has the highest sterol content.

GENERAL OBSERVATIONS

The loss of weight was most rapid in the first month, then the descent was gradual up to a week or two before death, when it again became rapid (fig. 2). Often the first rapid loss of weight was in itself fatal, death frequently occurring in the third or fourth week. Whipple stated that such rapid death is due to infection of the fistula, but that was not our experience. It seemed that after the first sudden loss in weight, the dogs began to compensate for the loss of bile. If this compensation broke down, death took place fairly promptly. In some of the dogs which lived for from four to five months there was only a slight loss during the second and third months. On the other hand if one includes the number of dogs dying within the first three to four weeks, the average length of life was probably about five weeks. Dogs which survived the first rapid decline usually lived for at least three and one-half months. These facts should be noted by surgeons who are tempted to "drain off the poisons" in cases of clinical jaundice.

The appetite was moderate and but little difficulty was encountered in making the dogs eat. Changes in diet, however, were not well tolerated, and often implied a period of starvation. The loss of weight brought about a certain lethargy in some cases, but most dogs remained playful and very active almost into the terminal stages. Some appeared unduly excitable and boisterous when taken from the cages for their daily exercise. We came to regard any lethargy or depression as an indication that something was wrong with the fistula. One dog gave birth to a litter of pups on the twenty-seventh day after operation and lived nearly four months longer. Death usually occurred without any characteristic findings and was apparently due simply to inanition and rapidly oncoming weakness. The diet was varied only slightly and was in general well tolerated, although it was impossible to avoid attacks of diarrhea. These attacks did not seem to be related to any changes in diet but could be fairly regularly induced by the addition of fat to the diet. On the other hand, a huge addition of fat might not cause any disturbance at all. The same condition in patients with biliary fistula was previously reported on by Andrews, Hrdina and Dostal.[29] It is

29. Andrews, E.; Hrdina, L., and Dostal, L. E.: Etiology of Gallstones: II. Analysis of Duct Bile from Diseased Livers, Arch. Surg. **25**:1081 (Dec.) 1932.

probably due to variations in the intestinal flora, which may or may not cause a fatty acid-containing stool.

The volume of the bile excreted varied widely for no apparent reason. The dogs were allowed water ad libitum, and the intake of fluids might have influenced the volume. The average output was from 6 to 20 cc. per kilogram of body weight per day. Whipple and his coworkers [30] stated that "variations in bile secretion are startling and inexplicable." Our experience was that when all the bile was drained to the outside the excretion was about one-third less than normal. In this observation Stadelmann,[31] Whipple and his associates [32] and others agreed. The average of our entire series was 10.4 cc. per kilogram per day. However, the unexplainable variations were extreme (from 3 to 23 cc. per kilogram per day). There was no tendency for the excretion to lessen in the latter periods of extreme cachexia (tables 1 to 4).

In the human being it appears that the biliary excretion is considerably less than this amount per kilogram. Pfaff and Balch [33] got 525 cc. per day from a patient with a biliary fistula. Ross [15] found that it varied between 505 and 725, averaging 556. Andrews, Hrdina and Dostal [29] placed it somewhat higher but within the same range. In Ross' [15] observations on one human subject there was an increase of about 50 per cent when bile was fed by mouth. In 1902 Brand [34] reviewed a large series of reports of biliary fistula, and his very extensive analysis showed that the average for man was from 500 to 1,100 cc. per day. In his report, as in most others, the weights of the patients were not given, but if they are taken to average about 70 kilograms, the average excretions would run between 7 and 17 cc. per kilogram per day, in most cases being much nearer the lower figure.

Similar violent fluctuations occurred in the quantities of the biliary constituents which were measured (tables 1 to 4). The cholesterol concentration appears to have no relation to that of the bile salts. Similarly, the amounts of cholesterol or bile salts excreted appear to have no relation to the concentration of the bile. There is apparently, as Wisner

30. Foster, F. M.; Hooper, C. W., and Whipple, G. H.: Metabolism of Bile Acids: Normal Fluctuation in Healthy Bile Fistula Dogs, J. Biol. Chem. **38**:367, 1919.

31. Stadelmann, E.: Ueber das Vorkommen von Gallensäuren Hippursäure und Benzoësäure in den Nebennieren, Ztschr. f. physiol. Chem. **18**:380, 1893.

32. Foster, M. G.: Hooper, C. W., and Whipple, G. H.: Metabolism of Bile Acids: Administration by Stomach of Bile, Bile Acids, Taurine and Cholic Acid to Show Influence upon Bile Acid Elimination, J. Biol. Chem. **38**:379, 1919.

33. Pfaff, F., and Balch, A. W.: An Experimental Investigation of Some of the Conditions Influencing the Secretion and Composition of Human Bile, J. Exper. Med. **2**:49, 1897.

34. Brand, J.: Beiträge zur Kenntnis der menschlichen Galle, Arch. f. d. ges. Physiol. **90**:494, 1902.

and Whipple [35] said, "a complete dissociation of the constituents of the bile." In a previous report [24] it was shown that in the case of the human being the bile collected in the morning was considerably less than that obtained in the afternoon or at night. These results agree with the findings of Whipple and of Ross. In the present experiments the amount collected during the day was inclined to be considerably larger than that at night, although the differences were not nearly so pronounced as in the human being.

A brief summary of the various theories of the causes of acholic cachexia is necessary in orienting oneself, but these theories will be discussed in detail along with the portions of our work having a bearing on them:

1. Anemia due to loss of pigment from the body.

2. Anemia due to inability to absorb vitamin D.

3. Acidosis due to loss of unbalanced ions in the bile.

4. Hemorrhages from gastric or duodenal ulcers produced by the lack of alkaline bile in the duodenum.

5. Fat starvation from inability to absorb fats in the absence of bile from the intestine.

6. Avitaminosis from inability to absorb vitamin D. With this must be considered the factor of anemia as well as the often reported factor of osteoporosis.

7. Disturbance in the calcium metabolism due either to loss in the bile or to inability to absorb calcium from the acholic intestine. The hemorrhagic disturbances often reported in the later stages have been associated with this possibility.

8. Lack of sterols in the body due either to loss in the bile or to inability to absorb them from the acholic intestine.

9. Loss of the bile acids.

ANEMIA DUE TO LOSS OF PIGMENT FROM THE BODY

In a considerable portion of the literature on acholic cachexia, it is said that an invariable accompaniment is the development of profound anemia, and many observers believe that this is a cardinal factor in the picture. Balfour and Ross,[7] Wangensteen,[1] Balderston,[36] Ross,[18] Pfaff

35. Wisner, F. P., and Whipple, G. H.: Bile Salt Metabolism: Variations in the Output of Bile Salts Pigments During Twenty-Four Hour Periods, Am. J. Physiol. **60**:119, 1922.

36. Balderston, S. V.: Anemia Associated with Biliary Fistula, Arch. Int. Med. **50**:223 (Aug.) 1932.

and Balch,[38] Seyderhelm and Tammann [37a] and Baumann [37b] reported clinical cases in which this factor seemed to be important. Balfour and Ross [7] cited one case in which an apparently complete fistula had been present for three years, and except for the fact that the patient's hemoglobin content was 35 per cent no other pathologic lesion was evident. In the one hundred and sixty-six cases reported by them, most of the patients who were cachetic were profoundly anemic. In the light of modern knowledge of the condition it seems reasonable to assume that the patients who were not cachetic had incomplete fistulas. Most of these authors, as well as many others, pointed out that administration of bile by mouth in varying amounts will bring about marked regeneration of the blood. Queen, Hawkins and Whipple [9] demonstrated how little bile is needed to keep an animal in normal health, and from our own experiences we feel inclined to believe that his minimum of 5 cc. per kilogram per day represents the upper rather than the lower limits of the average. On two different occasions we noted a sudden gain in weight in experimental animals with apparently complete fistulas. Although in each case it was subsequently shown that the gain in weight was due to a partial reestablishment of the common duct, bile was not evident in the stools, even by chemical tests, for several days.

While it seems the almost unanimous opinion of all workers that the anemia is due either to loss of pigment or to avitaminosis (which will be discussed later), there has been a definite opinion to the contrary expressed by Whipple and his associates.[38] In their experience anemia simply did not occur, provided the dogs were kept in good general condition and provided the fistulas were functioning properly. In their opinion, ascending infection is the most important factor, although intoxication of other sorts and faulty diet may have considerable influence. Some observers have studied the general type of blood picture and found that usually the hemoglobin fell considerably faster than the red count and that in many cases leukopenia was present as well. Lymphopenia has also been noted. These factors are hard to correlate with a picture of chronic septic anemia and suggest that damage to the liver rather than infection may play a rôle.

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37. (*a*) Seyderhelm, R., and Tammann, H.: Ueber die Blutmauserung: Die Gallenfistelanämie des Hundes, Ztschr. f. d. ges. exper. Med. **57**:641, 1927. (*b*) Baumann, W. (Göttingen): Ueber die Blutmauserung: Weitere Untersuchungen über die zur Entstehung der Gallenfistelanämie führenden Störungen, ibid. **75**: 401, 1931.

38. (*a*) Whipple, G. H., and Smith, H. P.: Bile Salt Metabolism: V. Proline, Tryptophane and Glycine in Diet, J. Biol. Chem. **89**:705, 1930. (*b*) Hawkins, W. B.; Sribhishaj, K.; Robscheit-Robbins, F. S., and Whipple, G. H.: Bile Pigment and Hemoglobin Interrelation in Anemic Dogs, Am. J. Physiol. **96**:463, 1931.

In order to evaluate the possibility that loss of pigment is a factor in producing anemia, one must review the salient points in the formation of pigment. Hemoglobin is the starting point, and the question is at just what step in its degradation its usefulness to the organism ceases. The first stage is the separation of the huge globin molecule. The residual hematin is an iron-bearing pigment closely related to bilirubin, which undoubtedly takes its origin from it by the removal of the single iron atom. An intermediate stage may be the highly toxic hematoporphyrin (said to be an isomere of bilirubin), which is thought by some to cause the toxic symptoms of jaundice, as it produces intense itching if injected into animals. Bilirubin is converted into biliverdin and then into urobilin and stereobilin, the possibly identical pigments found respectively in the urine and stools. Most students deny that there is any absorption or further utilization of the bile pigments from the intestinal tract. This is in direct opposition to the position of the bile acids, as the enterohepatic circulation of these, as shown by Whipple and his associates,[39] is an important feature in body economy. If hemoglobin is fed to an animal with a biliary fistula, there is a definite rise in the pigment content of the bile, but if bile pigments are fed this rise does not take place—direct evidence of their nonabsorption.[40] It appears, therefore, that after the blood pigments have lost their iron they are no longer capable of reconstitution into carriers of oxygen and hence represent a waste product. On theoretical grounds, therefore, one cannot expect that the interruption of any such process by the production of external biliary fistula will bring about any deficiency in hematogenesis.

Our results agree with none of those previously reported by other authorities except Whipple and his associates. In other words, in the animals which were carefully cared for, anemia of any degree simply did not occur. However, in some previous experiments in which we used preparations other than the Dragstedt cannula, massive hemorrhage from gastro-intestinal ulceration often produced profound anemia, and in other previous experiments severe anemia, obviously based on sepsis, was common.

Tables 1 to 4 show the blood picture of four dogs which survived for from four and one-half to five and one-half months with complete biliary diversion and died with the typical symptoms of cachexia cholipriva. Frequent blood counts and estimations of hemoglobin showed that the anemia was of trifling degree and did not approach in severity

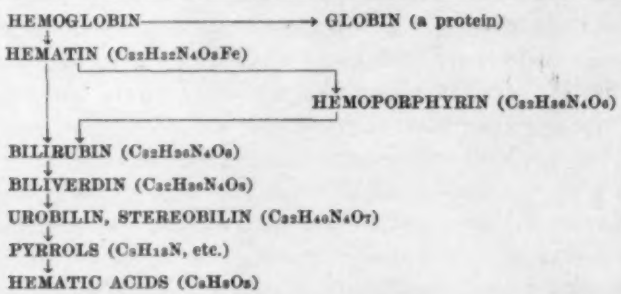
39. Foster, F. M.; Hooper, C. W., and Whipple, G. H.: Metabolism of Bile Acid: IV. Endogenous and Exogenous Factors, J. Biol. Chem. **38**:393, 1919.

40. Whipple, G. H.: Origin and Significance of the Constituents of Bile, Physiol. Rev. **2**:440, 1922.

the general cachexia as measured by loss of weight. In all animals the red cell count and the hemoglobin content were within the lower limits of normal up to the point of death, although a few days before death there was a slight fall in some of the dogs. Figure 2 is a graphic summary of the results. These findings are all the more striking when one remembers the amount of blood withdrawn from the animals for the various classical studies. In each case this amounted to about 600 cc. during the course of the experiments (from four to five months).

The average loss of body weight during the period was 33 per cent. The average loss of hemoglobin was 17.4 per cent and of red cells 17.8 per cent. If one ignores the terminal loss within the last few days before death, one can see that the average was the same for the last four months of life. The lowest red cell count was 4,200,000 per

TABLE 5.—*Schematic Representation of the Degeneration of Hemoglobin* *



* The formulas given are all tentative and taken from Mathews. The various pyrrols and hematic acids are definitely known.

cubic centimeter. One dog died with a red blood cell count higher than before operation, after having lost 41 per cent of body weight in five months. Balderston [36] found that there were changes in the size and shape of the red cells in acholic cachexia. We were not able to confirm this observation.

Studies of the fragility of the red cells were also made every four days in these dogs, and at no time was there the slightest change. The method used was Sanford's,[23] that of testing the degrees of hemolysis in saline solutions of various concentrations of salt. At no time during the entire experiment were there any deviations from the normal either as measured from the beginning of hemolysis or at its completion.

If, therefore, dogs may be carried through periods of acholic cachexia typical in every point and ending in death without the occurrence of anemia, one feels justified in agreeing with Whipple. He found that anemia did not occur in dogs kept alive by feeding them minimum amounts of bile for as long as four years. Our own experiments showed

that even in complete biliary deprivation anemia does not necessarily occur, and when it does it must be attributed to some complication, not necessarily to the direct deprivation of bile.

ACIDOSIS

Acidosis due to the loss of alkaline bile has been considered a factor in biliary cachexia by many observers. Since the time of Pavlov [41] this has been associated with the bony changes and other features of the

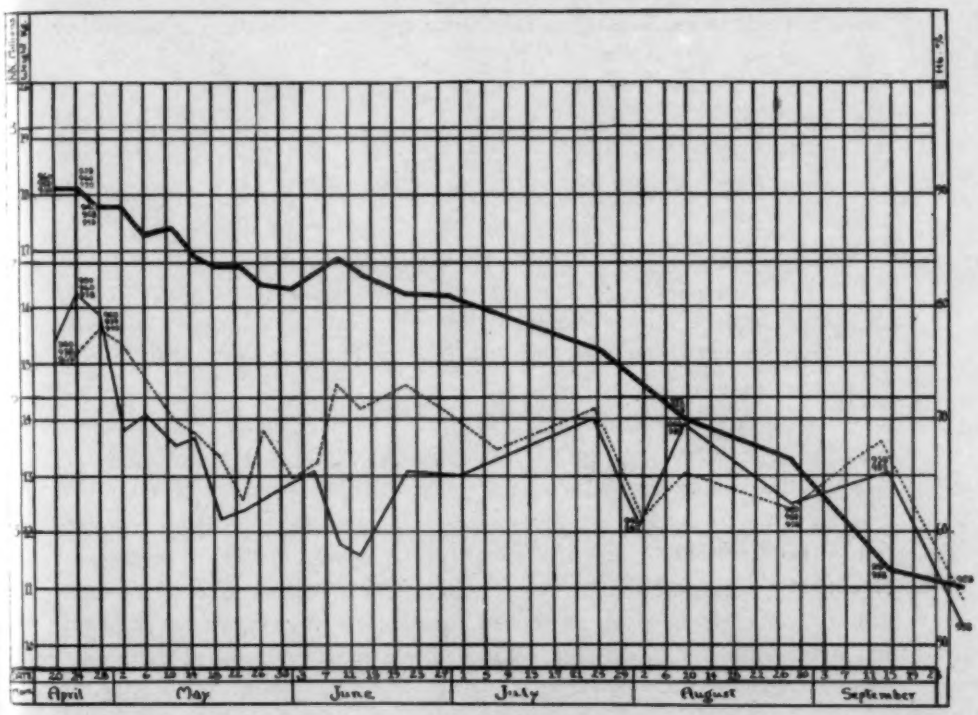


Fig. 2.—Average values on four dogs, showing the relation of anemia to acholic cachexia. The heavy solid line indicates the weight, the light solid line the red blood cell count, and the dotted line the hemoglobin content. Note the early initial slight drop and the maintenance of the level of the red cell count and the hemoglobin content until just before death. The loss of body weight was far more rapid and progressive.

disease. Balfour, Ross, Wangensteen and many other observers noted acidosis in clinical and experimental cases. Düttmann, in 1927,[42] sum-

41. Pavlov, I. P.: The Work of the Digestive Glands, translated into English by W. H. Thompson, ed. 2, London, C. Griffin and Company, 1910.

42. Düttmann, G.: Die Veränderung des Säure-Basengleichgewichtes nach Gallenfisteln und ihre Bedeutung bei der Entstehung der sogenannten porotischen Malacie, Beitr. z. klin. Chir. **139**:720, 1927.

marized the literature and discussed the relation of the condition to osteomalacia.

According to most of the early chemists, bile was either neutral or slightly alkaline to litmus (Hammarsten). When more accurate studies became possible, it was revealed how slight was this alkalinity. Previous studies on the p_H of liver bile have given rather a wide range of values. Okada [43] found that in the dog it ranged a trifle over 8. Düttman's figures, both for dogs and human beings, showed it a trifle lower. In the prolonged and detailed studies of Drury, McMaster and Rous, the usual finding was about p_H 8.2, although on standing the alkalinity might increase considerably. Neilson and Meyer [44] found the p_H of fresh bile from the liver to lie within this same range but emphasized the point that on standing it might go up to 8.4 or 8.6 and attributed this to loss of carbon dioxide. Drury emphasized the point that bile is a very well buffered solution and that addition of a considerable amount of acid is necessary to change its reactions appreciably. The recent investigations of Jones [45] called attention to the considerable buffer action of the large amount of sodium bicarbonate present, and he stated that this approximates that in pancreatic juice, which has long been known to contain so much that it froths violently on addition of strong acid.

Our studies have indicated that the p_H of bile, both that from the dog and that from the human being, is considerably lower if the bile is taken absolutely fresh.[46] It has generally run between 6.18 and 7. There seems to be a great lack of equilibrium, as the carbon dioxide concentration of fresh bile from the liver is usually over 100 in a series of nearly a hundred estimations in dogs. This carbon dioxide concentration at such a p_H gives of course a decidedly supersaturated solution, and great care must be taken in its collection to prevent its giving off large amounts of carbon dioxide. This occurs when the bile stands in the gallbladder, for then its carbon dioxide content is about one third as much in spite of considerable concentration.

Ross [15] found from 430 to 460 mg. per hundred cubic centimeters of chlorides in human bile drained from a fistula, and Wangensteen [1] was able to get about 0.4 Gm. of sodium chloride a day in bile from one of his patients. Bile obtained from a fistula, according to our experience

43. Okada, S.: On the Secretion of Bile, J. Physiol. **59**:457, 1915.

44. Neilson, N. M., and Meyer, K. F.: Reaction and Physiology of Hepatic Duct and Cystic Bile of Various Laboratory Animals, J. Infect. Dis. **28**:510, 1921.

45. Jones, K. K.: Comparison of Buffer Value of Bile and Pancreatic Juice Secreted Simultaneously, Proc. Soc. Exper. Biol. & Med. **28**:567, 1931.

46. Aronsohn, H. G., and Andrews, E.: Nonbacterial Cholecystitis: Mechanism of Acidification of Bile in the Gallbladder, Proc. Soc. Exper. Biol. & Med. **33**:89, 1935.

as well as that of others, contains about the same amount of chlorides as serum does, and therefore theoretically one might expect that the loss of chloride would more or less parallel the theoretical loss of chloride in a hemorrhage of equal amount. This certainly represents an upper limit of possible loss of chloride. It is quite clear, then, that the total possible loss of chloride falls far within the range that may be and is easily made up in the food. No comparison is possible with the extensive, rapidly fatal loss of chlorides in gastric fistula.[47]

No free base is found in bile, and all the sodium not present as carbonates or chlorides is bound to bile acids. The other electrolytes

TABLE 6.—*Data Showing the Acid-Base Equilibrium in Eight Dogs Studied for Periods of from Twelve to Eighty Days After Operation*

Days After Operation	Cholecystostomy 640		Cholecystostomy 639		Cholecystnephrostomy 745		Cholecystnephrostomy 678		Dragstedt Cannula 824		Cholecystnephrostomy 680		Cholecystnephrostomy 699	
	CO_2	Cl	CO_2	Cl	CO_2	Cl	CO_2	Cl	CO_2	Cl	CO_2	Cl	CO_2	Cl
(Normal values before operation)	% 42	294	% 40	300	% 36	294	% 32	282	% 36	...	% 41	305	% 46	294
4	42	296	42	294	29	299	40	306	33	...	48	274	39	277
8	40	297	40	272	26	299	34	294	35	...	27	311	43	250
12	42	307	38	327	23	305	42	289	29	...	29			
16	37	299	37	283	29	299	32	310	25	...	28	283		
20	33	...	31	349	32	310	27	305	36	...	33	316		
24	35	305	35	305	25	...	32	316						
28	27	305	30	371	30	...	30	316						
32	33	316	40	327	29	...	39	332						
36	46	310	46	305	21	...	33	321						
40	31	348	35	283	25	...	35	305						
44	31	310	34	327	41									
48	31	327	33	337										
52	36	337	42	300										
56	39	305	24	294										
60	42	310	34	310										
64	40	...	32											
68	35	...	42											
72	32	...	36											
76	36													
80	30													

are present in quantities too small to consider in relation to the normal dietary intake. Therefore there seems to be no theoretical reason to expect changes in the acid-base equilibrium as a direct result of loss of either anions or kations in the bile (table 6).

This has been exactly our experience. Eight dogs were studied for periods ranging from twelve to eighty days after operation, and the results are tabulated in table 6. The average carbon dioxide-combining power, according to Van Slyke and Cullen,[48] at the conclusion of the experiment was exactly the same as in the control estimations before the experiments began (39.5). The average chloride content (expressed

47. Dragstedt, L. R., and Ellis, J. C.: Fatal Effect of Total Loss of Gastric Juice, Proc. Soc. Exper. Biol. & Med. **26**:305, 1929.

48. Van Slyke, D. D., and Cullen, G. E.: Studies on Acidosis, J. Biol. Chem. **30**:289, 1917.

as chlorine [49]) before operation was 290 mg. per hundred cubic centimeters, and at the conclusion of the experiment was 293 mg. per hundred cubic centimeters, a change quite within the limits of experimental error. These animals were all on mixed diets containing much meat, and the onset of the cachexia was prompt and typical.

It seems justified, therefore, to assume that if the typical picture of cachexia cholipriva may be produced without changes in the acid-base equilibrium this factor is not fundamental, and that when reported by others it must be assigned to some intercurrent or indirect cause and must not be considered as a fundamental etiologic factor. While acidosis, as reported by many, may be a frequent accompaniment of acholic cachexia and may explain some of its manifestations, it seems wisest to attribute it to infection of the fistulous tract rather than to loss of bile.

PEPTIC ULCER

To all students of biliary physiology the duodenal ulcer has been the cause of many disappointments. It is an old and familiar story that just about the time that an experiment reached the critical stage, after much time and energy had been expended, sudden death occurred because of massive hemorrhage from the ulcerated stomach or duodenum. This danger is ever present in all experiments in which there is an absence of bile from the duodenum, whether produced by fistula or by obstruction of the common duct. The onset of these ulcers is usually prompt, generally occurring in the second week.[50] The ulcers are usually in the duodenum but not seldom in the pyloric portion of the stomach. They vary all the way from minute erosions to large callous ulcers typical of those observed in the clinic. Perforation of the deeper type is not uncommon, and hemorrhage is distressingly frequent. In the hands of most surgeons the administration of alkali has been of little value, although Kim and Ivy [50] reported that 1 Gm. of gastric mucin a day will prevent duodenal ulcer.

In our own experience, in animals with either jaundice or biliary fistula such ulcers have been distressingly frequent, although no records are available as to the percentage of their incidence. Bollman and Mann [51] in an extensive study found that they occurred in 60 per cent of the cases of ligation of the common duct. Kapsinow, Engle and Harvey [19] found seventeen in forty-three dogs on which cholecystneph-

49. Whitehorn, J. C.: Simplified Method for the Determination of Chlorides in Blood or Plasma, J. Biol. Chem. **55**:499, 1921.

50. Kim, M. S., and Ivy, A. C.: Prevention of Experimental Duodenal Ulcer by Feeding Neutral Gastric Mucin, J. A. M. A. **97**:1511 (Nov. 21) 1931.

51. Bollman, I., and Mann, F. C.: Peptic Ulcer in Experimental Obstructive Jaundice, Arch. Surg. **24**:126 (Jan.) 1932.

rostomy had been performed. Kim and Ivy found ulcers in 10 per cent of dogs in which the common duct had been tied and in 60 per cent of those in which the Rous fistula was used. Berg and Jobling,[52] using a Rous fistula, found peptic ulcers in thirteen of twenty-three dogs. These figures represent a considerably higher incidence than our experience indicates but are in accord with the fact that the Rous type of fistula with the cannulation of the common duct close to the duodenum is especially provocative of ulcer. Kim and Ivy suggested that the mechanical irritation of the tubing in this neighborhood is a factor. This observation is interesting in view of the finding of Elman and Hartmann [17] that a fistula alone causes ulcers in but few cases. In our own hands the Rous fistula was conspicuously unsuccessful technically and, as stated previously, caused many ulcers. Elman, as well as Rous, had considerable technical success and reported few ulcers.

Berg and Jobling [52] suggested that the general condition of the dog and the hygienic conditions under which it is kept are important factors. He found that ulcers developed in 100 per cent of dogs under ordinary management, but that by providing special care of a general type this percentage was reduced to 30. He was able to construct smoothly functioning Rous fistulas, and but few ulcers occurred.

Our experience in the use of the Dragstedt cannula proved quite surprising, to us at least. Instead of losing a high percentage of animals because of the development of ulcers, we did not lose a single one of over thirty dogs. Careful postmortem examination and constant examination of the stools for blood (chemical as well as gross) gave negative results in all cases. In not a single dog did either gastric or duodenal ulceration occur.

The explanation of this phenomenon is difficult. The cachexia was usually of a very advanced grade, and most of the animals that lived long lost over one third of their body weight. Certainly their "general condition," in the sense discussed by the aforementioned authors, was the worst possible. It appears necessary to reconsider our former hasty conclusion that lack of alkaline bile is the sole factor. In the first place the alkalinity of bile is minimum although considerable buffering power is present, as was discussed before. McRoberts [53] studied the p_H of the duodenal contents following exclusion of bile and found that it was changed only to a minimum degree. In fact the change was so negligible that he concluded that the buffering action of the pancreatic juice was sufficient to prevent any acidity of the duodenal contents

52. Berg, B. N., and Jobling, J. W.: Biliary and Hepatic Factors in Peptic Ulcers: An Experimental Study, Arch. Surg. **20**:997 (June) 1930.

53. McRoberts, J. W.: Effect of Exclusion of Bile on Reaction of Duodenal Contents, Proc. Staff Meet., Mayo Clin. **7**:453, 1932.

even in the total absence of bile. Jones [45] found that the buffering power of the pancreatic juice considerably exceeded that of the bile, and that the two seemed to act in a compensatory manner. When that of the bile fell, that of the pancreatic juice rose, and vice versa.

If it is possible, then, to carry dogs as a routine through the whole course of acholic cachexia without the formation of ulcers by any method, it seems reasonable to attribute the well known tendency toward ulceration to some concomitant feature and not to lack of alkali alone. While obviously this must be an important feature, it just as obviously cannot be the sole one. Possibly the suggestion of Still and Carlson [54] is relevant. They showed that damage to the liver had a potent effect on the motility of the stomach, and it is quite conceivable that as damage to the liver was minimal in our dogs its absence may help to account for lack of peptic ulcers. Heller [55] and many others have reported a hemorrhagic diathesis in the presence of a complete biliary fistula. This may be cured by the addition of bile to the diet. Some have considered this as a manifestation of damage to the liver and others as due to a lack of calcium and to be related to the osteoporosis. However, such a condition is often suggested by the gross appearance of the ulcers seen in biliary diversion, as multiple minute punctate submucous hemorrhages are a common finding.

FAT STARVATION

On the authority of Claude Bernard we assumed that the digestion of fat is totally abolished in the absence of bile from the intestinal tract, and in spite of the obvious fact that his experiments did not justify such a sweeping conclusion one constantly encounters the same statement today. Pflüger,[56] Dastre [57] and later Levin [58] arrived at a similar conclusion, using the same general criterion, i. e., absence of milky chyle in the lymphatic vessels draining the acholic portion of the intestine. The conclusion is backed also by the well known clinical occurrence of fatty stools in the case of jaundice and of biliary fistula, as well as by the intolerance of fats and the frequent attacks of diarrhea due to the presence of fatty acids. While most workers have felt that the

54. Still, K. S., and Carlson, A. J.: Motor and Secretory Activity of Stomach During Acute and Chronic Obstructive Jaundice in Dogs, Am. J. Physiol. **74**: 34, 1929.

55. Heller, E.: Hämorrhagische Diathese ohne Ikterus bei vollständiger äusser Gallenfistel, Deutsche Ztschr. f. Chir. **235**:667, 1932.

56. Pflüger, E.: Die Resorption der Fette vollzieht sich durch, dass sie in wässrige Losung gebracht werden, Arch. f. d. ges. Physiol. **86**:1, 1901.

57. Dastre, A.: Du rôle de la bile dans la digestion des matières grasses, Compt. rend. Soc. de biol. **4**:782, 1887.

58. Levin, I.: Ueber den Einfluss der Galle und des Pancreassaftes auf die Fettresorption in Dünndarm, Arch. f. d. ges. Physiol. **63**:171, 1896.

digestion of proteins and carbohydrates was normal or nearly so in the absence of bile, it is quite clear that the emulsification and absorption of fat are seriously retarded. Rachford [59] showed that the action of pancreatic lipases was increased threefold by the addition of bile and that the constituents of the bile which had this function were the bile salts. He was able to produce in vitro the digestive powers of bile quantitatively with pure bile salts. Von Fürth and Schütz [60] showed that bile, added to pancreatic secretions in about the proportion found in the intestine, increased their fat-splitting powers ten times.

In spite of all this evidence, there is just as clear proof that the power to utilize fats in the absence of bile from the intestine is not totally lost. In the first place, animals dying from jaundice or a complete biliary fistula do not lose all their fats and in the former case may live for more than a year. If absence of bile causing fat starvation is the important factor in such cachexia, it is difficult to explain why jaundice is so well tolerated and the fistula is not. Furthermore direct evidence is not lacking. While alimentary lipemia of a high degree cannot be produced in animals with fistulas, a slight postprandial rise can be seen. Umber was unable to recover more than about one half of the ingested fat from the stools, and bacterial action sufficient to account for such a destruction seems most unlikely. Munk's [61] elaborate studies of the question indicate that in favorable circumstances as much as one half of the fat may be absorbed and that usually from 10 to 20 per cent can be accounted for in no other manner except by assuming its absorption and utilization.

On the other hand, there is considerable recent literature indicating that direct absorption of fats into the blood stream is possible. The method recently demonstrated by Verzár and Kúthy,[62] however, requires the presence of bile in the intestine, and it seems more rational to assume that absorption of fat from the acholic intestine in diminished amounts must take place through the lacteals (fig. 3).

Our studies justify the general conclusions of the last authors on several grounds: 1. Postmortem examination fails to show a specific

59. Rachford, B. K.: The Influence of Bile on the Fat Splitting Properties of Pancreatic Juice, J. Physiol. **12**:72, 1891.

60. von Fürth, O., and Schütz, J.: Ein Beitrag zur Methodik der Versuche über Fettresorption aus isolierten Darmschlingen, Beitr. z. chem. Phys. u. Path. **10**:462, 1907.

61. Munk, I.: Ueber die Resorption von Fetten und festen Fettsäuren nach Ausschluss der Gallen vom Darmkanal, Virchows Arch. f. path. Anat. **122**:302, 1890.

62. Verzár, F., and Kúthy, A.: Die Verbindung der gepaarten Gallensäuren mit Fettsäuren und ihre Bedeutung für die Fettresorption; Löslichkeit und Diffusibilität, Biochem. Ztschr. **210**:265, 1929.

Fig. 3.—Photomicrograph (× 25) of the liver from a dog that survived ligation of the common duct sixteen months. Note the almost complete replacement of the parenchyma with fat.

loss of fats. Much fat is found, and the distribution is normal. Furthermore, the liver may often show an increase in fat. 2. A slight alimentary lipemia is possible. 3. The survival of certain jaundiced animals may be prolonged. One, in particular, lived for sixteen months and weighed more at death than before the operation. The most striking aspect at autopsy was the extreme obesity and the extensive fatty infiltration of the liver. The liver was nearly white, and microscopic examination showed that nearly all the parenchymatous tissue had been replaced by fat (fig. 3). Although measurement was impossible, there is no doubt but that this animal contained much more fat after sixteen months of absence of bile from the intestine. Such a picture is certainly incompatible with the theory that in the absence of bile there is inability to absorb fats from the intestinal tract.

We intended to study the fat balance in several of the dogs, but on account of the extreme difficulty in collecting the specimens this proved impossible. In order to keep dogs in good health, periods of

TABLE 7.—*Effect of Fifty Grams of Fat Administered Orally on the Fat Content of the Blood*

	Milligrams per Hundred Cubic Centimeters			
Control	77	83	107	127
12 hours	115	88	125	133
18 hours	86	88	125	136
4 days	99	77	107	99

exercise outside the cages were necessary, and when the stools were liquid, as they often were, many were lost or contaminated with material from the floors of the laboratory. However, a series of seventy-nine estimations of blood fats were made on four dogs extending over their periods of cachexia (tables 1 to 4). These showed clearly that there was no lack of fat in the body, as the values all fell within the normal limits. Even dogs in the last stages of cachexia showed a fat content of the blood of about 0.1 per cent.

Four dogs were submitted to tests for alimentary lipemia. Fifty grams of fat was given by mouth. In all four a rise occurred in the blood fats, and in two this was considerable. The rise in one case was from 77 to 115 mg. per hundred cubic centimeters. While the rises were not comparable to those that occur in normal dogs, they indicate that in the presence of a biliary fistula some fat is absorbed.

Four other dogs with biliary fistulas were subjected to exploratory laparotomy and no whitish lacteals could be found, but such changes in the blood fats as are seen in table 7 would probably not have altered the gross appearance of the lymph. Nevertheless, there is a possibility that the fat may be absorbed directly into the blood stream.

Fig. 3.—Photomicrograph (× 25) of the liver from a dog that survived ligation of the common duct sixteen months. Note the almost complete replacement of the parenchyma with fat.

Thus while it is undoubtedly true that absorption of fat is markedly diminished in acholic cachexia, it is clear that moderate amounts are absorbed and that actual fat starvation does not take place.

AVITAMINOSIS

As a corollary to the theory that there is a lack of fat absorption goes the concept that fat-soluble vitamin, a sterol, is not absorbed from the intestine in the absence of bile. This attractive hypothesis is also closely related to the factor of anemia and to the frequently reported disturbances in calcium metabolism and associated osseous changes. Furthermore, a tremendous amount of evidence for this theory has been built up on the basis of careful experimental studies. The factor of anemia has been discussed, and the disturbances in calcium metabolism will be considered separately.

The effects of viosterol on various manifestations in an animal with a biliary fistula have been studied by many observers, and a definite correlation has been reported almost unanimously. The apparently overwhelming nature of the evidence presented, together with the utterly negative results of our experiments, warrants a review of the subject. Seifert,[63] Seyderhelm and Tammann,[64] Emerson,[65] Murakami,[66] Heymann,[67] Greaves and Schmidt,[68] Dietrich,[69] Heller,[55] Seyderhelm and Tammann,[37a] Baumann,[37b] Takasu [70] and Whipple and his associates [38b] reported experiments indicating a direct relationship of acholic cachexia to lack of fat-soluble vitamin. Evidence of various sorts was included. Tammann [64b] found that the osteomalacia associated with acholic cachexia could be prevented and cured by injection of activated ergosterol. Later,

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63. Seifert, E.: Zur Frage der porotischen Malazie nach Gallenfisteln, Beitr. z. klin. Chir. **136**:496, 1926.

64. (*a*) Seyderhelm and Tammann.[37a] (*b*) Tammann, H.: Ueber die Beeinflussung der porotischen Osteomalazie nach Gallenfistel durch das D-Vitamin, Beitr. z. klin. Chir. **142**:83, 1928.

65. Emerson, W. C.: Distribution of Calcium in Jaundiced and Acholic Dogs, J. Lab. & Clin. Med. **14**:122, 1928.

66. Murakami, K.: Ueber die Gallensäurebildung; Avitaminosen und Gallensäure-ausscheidung in der Galle, J. Biochem. **9**:321, 1928.

67. Heymann, W.: Untersuchungen über die Phosphatstoffwechselstörung bei Rachitis; über Rachitis und Tetanie bei Gallenfistelhunden, Ztschr. f. Kinderh. **54**: 201, 1933.

68. (*a*) Greaves, J. D., and Schmidt, C. L. A.: Studies on Calcium and Phosphorus in Bile Fistula Dogs, Proc. Soc. Exper. Biol. & Med. **29**:373, 1932; (*b*) The Rôle Played by Bile in the Absorption of Vitamin D in the Rat, J. Biol. Chem. **102**:101, 1933.

69. Dietrich, H.: Die porotische Malacie nach Gallenfistel, Beitr. z. klin. Chir. **134**:530, 1925.

70. Takasu, M.: Experimentelle Studien über die acholische Kachexie, Deutsche Ztschr. f. Chir. **224**:240, 1930.

with Baumann,[37b] he showed that iron had little effect in acholic anemia. Liver extracts were of slight benefit. However, irradiation of the animals helped more, while irradiated bile was considerably more potent than normal bile. Heller[65] found that administration of vitamin D prevented the hemorrhagic changes. Murakami found that olive oil had no effect on the secretion of bile acids, while viosterol raised it fourfold. (Whipple had previously shown the same result.) Heymann[67] reported that osteomalacia occurring in puppies with biliary fistulas is curable by the administration of viosterol. The previously mentioned experiments of Greaves and Schmidt,[68b] indicating that a phosphorus-calcium balance was restored to osteoporotic animals by the administration of viosterol are pertinent to this subject.

It has been reported by some that the blood calcium of dogs with biliary fistulas may be raised by the subcutaneous injection of viosterol. That this is impossible has been not only our experience but that of all workers in the field of vitamins, for the blood calcium levels of normal dogs cannot be raised by this means. Three experiments of this type convinced us of the futility. The first experiment consisted of feeding a dog with a biliary fistula 20 cc. of viosterol in oil 250 D. The effect on the blood calcium was nil. As controls two other normal dogs were each given the same dose, and the results were negative. This dose was said by a colleague who had used it previously to be about two thirds the lethal amount for a dog and that even the lethal amount would not cause a rise in blood calcium. It seems rational then to discard all experiments in which dogs have been used to test the effect of viosterol on the blood calcium unless there was a profound lowering of the calcium in the first place. It is well known that parathyroidectomized dogs respond to viosterol, but only if the blood calcium content is in the same range as that in the case of tetany.

There is also considerable literature on the osteoporosis caused by jaundice, in which the same factors are acting. This condition was reviewed by Buchbinder and Kern,[71] who like Heymann[67] and others thought that it was rather typical rickets.

With this apparently overwhelming evidence at hand, it is difficult to explain our results. They were, briefly, that no benefit occurred from the administration of viosterol in apparently adequate doses. There was in our animals no anemia or osteoporosis to combat, and the only way of measuring the effect of the vitamin was to weigh the animals and to see if it prolonged life. As can be seen from figure 4, it had not the slightest effect.

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71. Buchbinder, W. C., and Kern, R.: Experimental Obstructive Jaundice: I. Growth Factor in Defective Calcification, Arch. Int. Med. **40**:900 (Dec.) 1927; Blood Calcium Deficiency in Experimental Obstructive Jaundice, Am. J. Physiol. **80**:273, 1927.

The loss of body weight proceeded at the same general rate as in control animals, and life was not prolonged.

One curious feature may be worth noting, that is, the profound dependent terminal edema that occurred in four dogs of the series to which viosterol was administered. The edema was marked in all four paws and the anterior abdominal wall. In view of the fact that edema in a dog is an unusual occurrence and is produced experimentally only with considerable difficulty, two of these animals were studied by Dr. L. Leiter, who contributed the following data: The blood proteins

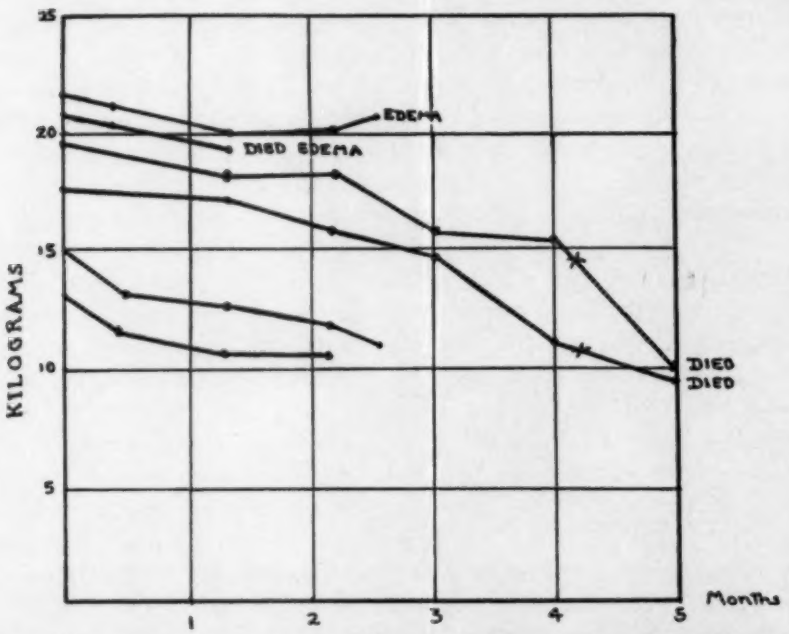

Fig. 4.—Chart of the body weights of six dogs with biliary fistula, to which viosterol was given hypodermically. The dogs with the two longest weight curves were given viosterol only after the point on the curve marked X. Others received it from the beginning of the experiment. Loss of weight ocurred at the same rate in the experimental animals as in the controls (fig. 2).

were only moderately lowered, being just about at the lower threshold of normal. The kidneys were normal at autopsy, both grossly and histologically. We have no explanation to offer for this phenomenon, and none of our animals except those treated with viosterol became edematous.

One dog, on the seventeenth postoperative day, had a single tetanic convulsion lasting about fifteen minutes. At this time the blood calcium was 12.4, the highest found at any time in his course; at the same time

a corneal opacity developed, which was attributed to avitaminosis by an ophthalmologist. However, the opacity disappeared spontaneously within ten days, and the dog survived for three months longer. This incident shows how easily data on avitaminosis may be misinterpreted.

Four other animals treated with viosterol showed marked increase in weight and general well-being. The coats became glossy and the appetite increased. Each of these animals was found to have an accessory duct, or the old ones reestablished, and to have small amounts of bile in the stools, which of course was the cause of the recovery. Such accidents may explain some of the previously reported results but certainly not all of them in the hands of many careful workers. On the other hand it does not seem exactly logical to assume, as many workers have, that just because viosterol may cure some of the manifestations of acholic cachexia, lack of viosterol is the direct cause of it. According to such logic, if, for instance, malaria is cured by quinine, it must be caused by lack of quinine! Whipple and his associates [38b] were careful not to reason thus, and although they reported that viosterol improved the blood picture in the cachetic dogs, they did not state that lack of it is the cause of the anemia. Viosterol is a powerful stimulant to osseous deposition, and the fact that it helps osteoporosis is not proof that lack of it causes the osteoporosis.

DISTURBED CALCIUM METABOLISM

Disturbances in calcium metabolism have been reported on by many authorities, some of whom considered it a direct result of avitaminosis, while others, beginning with Klinke, postulated inability to absorb calcium from the acholic intestine. The frequency with which osteoporosis has occurred in acholic cachexia is shown by the long series of papers on the subject.

Gilbert [72] first called attention to the possibility of serious loss of bile in cases of external drainage and spoke of this excretion as a specific function of the liver. On the other hand, many observers have found that the calcium of the bile from the liver usually fell within the range of that of the blood, although it is often slightly higher. In our laboratory in a series of sixteen dogs it averaged 13 mg. per hundred cubic centimeters. In the usual concentration in the gallbladder this paralleled the rise in the total solids for short periods such as fall within the time the bile ordinarily remains in the viscus.[73] Although in inflam-

72. Gilbert, E.: Ueber die Kalkausscheidung durch die Galle, Ztschr. f. d. ges. exper. Med. **53**:539, 1924.

73. Andrews, E.; Schoenheimer, R., and Hrdina, L.: Etiology of Gallstones: I. Chemical Factors and the Rôle of the Gallbladder, Arch. Surg. **25**:796 (Oct.) 1932.

matory conditions rapid absorption may occur [74] and in prolonged obstruction excretion is known to occur from the mucosa,[75] it seems safe to assume that in the normally functioning viscus no change in calcium content occurs except that incident to the concentration of the bile. If the usual volume of bile is from 10 to 20 cc. per kilogram of body weight, it is easily calculated that the average dog might lose from 100 to 300 mg. of calcium per day in drainage through a biliary fistula. If absorption is normal, this amount seems insignificant compared with the intake.

While Gilbert [72] found that the amount of calcium in the bile was about two thirds of that in the urine and that this secretion of calcium was not dependent on that in the urine, the large amount found in isolated segments of the intestine suggests that the major organ for the excretion of calcium is the intestine and not the kidney. Fecal calcium is usually far in excess of that in the urine. Thus in order to assume that disturbances in calcium metabolism are due to inability to absorb calcium directly it is first necessary to get concrete proof that such inability exists, and such proof is utterly lacking. Von Beznák [76] offered some evidence on this score. He showed that in dogs distinct alimentary calcemia was produced. Furthermore, passage of this blood through the liver did not change its calcium content. In normal dogs the content of the portal blood is the same as that of the blood in the general circulation, but after biliary diversion it was less. These experiments seem conclusive, but the changes reported might be considered as lying within the limits of experimental error.

On the other hand, Brougher [77] noted that the development of parathyroid tetany was much delayed by ligation of the common duct and assumed that this might be explained by an actual increase in the absorption from the intestine. Heymann [67] made biliary fistulas in puppies, which normally produce a condition very like rickets. He found that this condition was alleviated by irradiated ergosterol but not by calcium, and it seemed logical to assume that therefore the simple absence of bile from the intestine did not interfere with the absorption of the

74. Andrews, E., and Hrdina, L.: Absorption of Calcium from the Gallbladder, Am. J. M. Sc. **181**:478, 1931.

75. Phemister, D. B.; Day, L., and Hastings, A. B.: Calcium Carbonate Gallstones and Their Experimental Production, Ann. Surg. **94**:595, 1932.

76. von Beznák, A.: Der Einfluss der Galle auf die Resorption des Calciums, Arch. f. d. ges. Physiol. **228**:604, 1931.

77. Brougher, J. C.: Effect of Ligation of the Common Bile Duct upon the Appearance of Tetany in Thyroparathyroidectomized Dogs, Am. J. Physiol. **84**: 39, 1928.

calcium.[65] Sekitoo [78] showed that there was a definite decrease in blood calcium in rabbits with biliary fistulas, and that this could be corrected by the administration of bile salts by mouth. Fuziwara [79] showed that the addition of bile to the diet causes a dog to excrete more calcium in the bile and less in the stools. Rose and Kohn stated the belief that in the absence of bile more calcium is absorbed and attributed this to the fact that much calcium may be bound in insoluble compounds with the bile acids in the normal person.

Many observers, including ourselves, have found that the blood calcium and the blood phosphorus were normal in subjects with biliary fistulas. This is not exactly confirmed in our series of eighty estimations of blood calcium (tables 1 to 4). Although the figures toward the end are perhaps within the range of normal, it is quite clear that there is a decided change. In the period of preoperative control the average was about 12 mg. per hundred cubic centimeters and it had as a rule dropped to about 9 mg. in from four to five months. Neither figure by itself is significant, but if the entire series is plotted on a chart a fall is evident that is entirely beyond the limits of experimental error. Thus some disturbance in the calcium metabolism is evident. Thus decalcification of the skeleton, if it occurs, must be studied on the basis of the careful measurement of intake and output. This was done by Greaves and Schmidt, who demonstrated in rats and dogs that there was a negative phosphorus and calcium balance in the case of biliary fistula and that this returned to normal after the administration of viosterol and minute amounts of bile salts by mouth. Similar experiments on the human being by King, Bigelow and Pearce [80] gave similar results.

The evidence, while not complete, thus seems to point decidedly to a distinct disturbance of calcium metabolism in the case of biliary fistula. It is difficult to explain our results, which seem only to complicate the picture. These may be summed up in a word or two. In dogs with normally functioning biliary fistulas, in the absence of anemia, infection, periods of jaundice and other complications, osteoporosis did not occur. Two photomicrographs are shown, one representing the longest reported survival of a dog with a complete biliary fistula without accessory feeding (five and one-half months), and the other the longest reported survival of an adult dog with complete jaundice

78. Sekitoo, T.: Ueber den Einfluss der Gallensäure auf den Calciumstoffwechsel, J. Biochem. **12**:59, 1930; Beiträge zur Kenntnis der Glykocholeinsäure aus Kaninchengalle, Ztschr. f. physiol. Chem. **199**:225, 1931.

79. Fuziwara, K.: Ueber den Einfluss der Gallensäure auf den Calciumstoffwechsel: Calciumausscheidung im Kot bei Zufuhr von Cholsäure, J. Biochem. **13**: 465, 1931.

80. King, J. H.: Bigelow, J. E., and Pearce, L.: Experimental Obstructive Jaundice, J. Exper. Med. **14**:159, 1911.

(sixteen months). As can be seen, there is not the slightest sign of lacunar absorption, nor is there any thinning of the cortex of either bone. Roentgen studies in other cases have failed to show evidence of osteoporosis.

If it is possible to carry dogs through the entire course of typical cachexia cholipriva without osseous changes, one feels entitled to assume that these do not represent integral parts of the picture but are due to complications. In most of the previously reported cases both in human subjects and in animals the fistulas have been incomplete, as indicated by the long survivals. It may therefore be that osteoporosis in such cases is simply a manifestation of general cachexia and part and parcel of the widespread degenerative changes in all the organs. Many of the animals have been caged and many of the human subjects bedridden, and ordinary atrophy of the bones and muscles from disuse

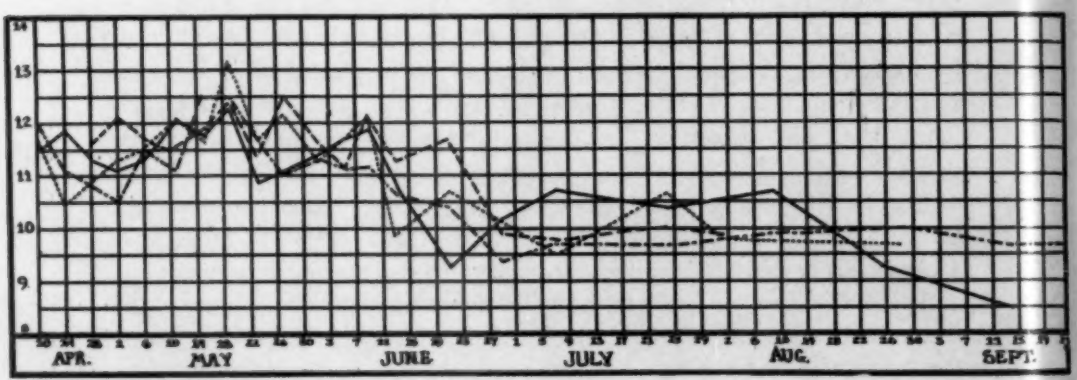

Fig. 5.—Chart showing the blood calcium curves of four dogs with acholic cachexia. Note the slight but definite lowering in all instances. The values are given in milligrams per hundred cubic centimeters. The broken line represents dog 940, the dot and dash line dog 958, the solid line dog 959, and the dotted line dog 960.

is possible. In any long continued severe disease osseous atrophy usually occurs, and parallels could easily be drawn in the clinic with such diseases as cancer, tuberculosis and pernicious anemia, in which prolonged invalidism or even old age has shown in roentgenograms conditions at least as typical as those often shown as being peculiar to biliary cachexia.

On the other hand, in the case of jaundice and of biliary fistula extreme osteoporosis may occur in the absence of bile from the intestine much too rapidly to permit these explanations. An alternative theory has been suggested by Düttmann,[42] who attributed osteoporosis to acidosis. Although the changes in the acid-base equilibrium reported in his experiments would not ordinarily be considered severe enough

Fig. 6.—Photomicrograph (× 18¾) of bone from a dog which survived fifteen months with complete biliary obstruction. Note the complete absence of osteoporosis.

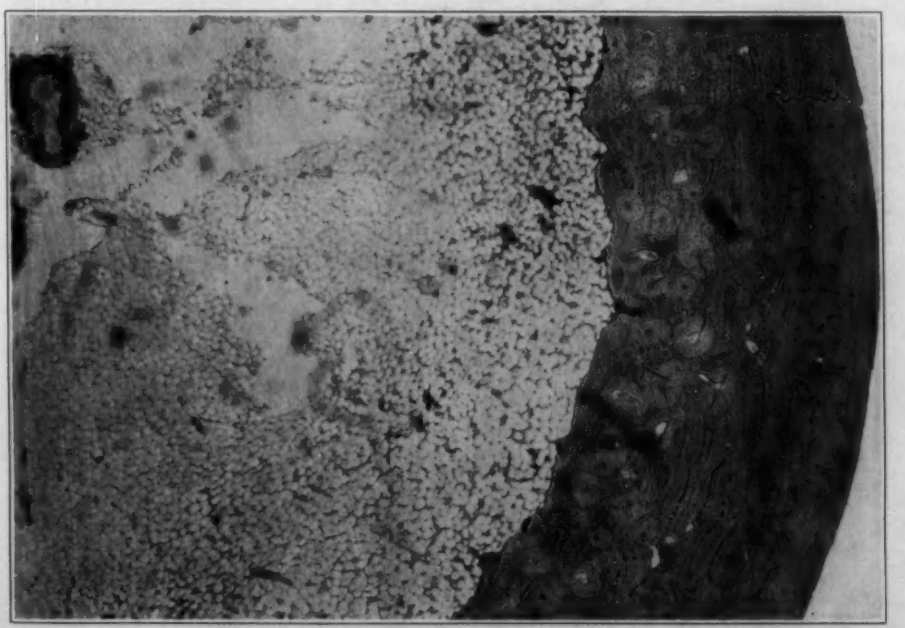

Fig. 7.—Photomicrograph (× 18) of bone from a dog which survived five months with complete biliary fistula.

to cause loss of calcium, much wider fluctuations have been found by other observers. Calcium carbonate is more soluble in acid mediums. Hastings and his associates [81] presented tables and equations enabling one to predict its solubility at various concentrations of other electrolytes at various values of p_H. Bodansky, Jaffe and Chandler [82] showed that extreme decalcification may be produced by the administration of phosphorus, which does not necessarily raise the level of the blood calcium which is controlled largely by the renal threshold. Later they produced typical decalcification in animals by acidosis caused by other means and made it clear that a negative calcium balance results in any condition of prolonged acidosis. In view of the fact that an association of acidosis with acholic cachexia has been reported by many authors, this seems to offer a ready explanation of the decalcification which may accompany the cachexia. As we stated previously, we believe that acidosis results from infection of the fistula or from damage to the liver and that the absence of these features in our experiments may account for the absence of osseous changes so often said to be typical.

CHOLESTEROL

The question of the absorption of sterols from the acholic intestine is intimately related to the theory of lack of vitamin D. If it is true that bile salts are necessary to absorb lipoids as they have been said to be needed to absorb fats, it is clear that there should be a decided lack of sterols in the organism under such conditions. This has not proved true in our experiments. While it is well known that the blood cholesterol content in the dog averages considerably higher than in man, the normal fluctuations are very wide. The uncertainty and inaccuracy of the methods usually applied for its estimation are perhaps partly accountable for these apparent fluctuations. Accurate cholesterol estimations can be made by only one method, i. e., the gravimetric one of precipitation with digitonin and weighing. This is impossible in using specimens as small as samples of blood necessitate (or even samples of bile). Therefore one of the various modifications of the Autenrieth-Funk color reaction is used, and in our hands the percentage of error was at least 20 per cent. We were never able to attain the degree of accuracy recently reported by some observers, who claimed that they had reduced this percentage of error to less than 3. The

81. Hastings, A. B.; Murray, C. D., and Sendary, J.: Studies of the Solubility of Calcium Salts, J. Biol. Chem. **71**:731, 1931.

82. Bodansky, A.; Jaffe, H. L., and Chandler, J. P.: Serum Phosphatase Changes in Calcium Deficiency and in Ammonium Chloride Osteoporosis, Proc. Soc. Exper. Biol. & Med. **29**:871, 1932. Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: Serum Phosphatase of Non-Osseous Origin; Significance of Variations of Serum Phosphatase in Jaundice, ibid. **31**:107, 1933.

figures in tables 1 to 4 must be interpreted in this light. Nevertheless, even allowing for such errors in method, it is seen at once that there is most decidedly not a lack of sterols that could possibly be interpreted as "sterol starvation." The blood cholesterol tends to be slightly lower in the latter periods of cachexia, but significant falls are totally absent. In all the dogs the levels of blood cholesterol fell within the lower limits of normal, and in two of them a higher level was found during the last month of life than in the controls before operation.

The phenomenon of the *Estersturz,* which recently was explained by Gardner and Gainsborough,[83] was not evident in our studies as the experimental periods were too short. It is well known that at the onset of either obstructive jaundice or biliary fistula there is a fall in the blood cholesterol, which later returns to a normal level and still later to levels about 50 per cent above normal. This is due to the loss of the absorbing power from lack of bile in the intestinal tract and to the consequent fall in the cholesterol esters to almost zero. The more recent work of Garside,[84] on the other hand, showed a distinct rise in the early stages. The failure of our animals to show hypercholesteremia in the later stages of the cachexia is a point of special interest which will be noted later.

Further fluctuations in the later stages of the cachexia are probably related to periods of starvation from distaste for food. It has been known for many years that starvation is a most potent factor in raising the blood cholesterol, and this phenomenon is quite characteristic of so-called war edema and hunger edema. At any rate, there is no indication from any of our studies that the dogs at any time had hypocholesteremia.

The cholesterol in the bile showed similar fluctuations which are only in part accounted for. These changes are not related to changes in the rate of secretion of the bile or in its concentration, or to the rate of secretion or to the concentration of the bile salts. Figures 8 and 9 give a graphic representation of data gathered from tables 1 to 4. Whether one calculates the percentage of cholesterol in the bile or measures the amount secreted per day, it can be seen that the fluctuations are wide and apparently inexplicable. However, the curves in general do not show any evidence of lack of sterols in the organism. In some cases concentrations and rates of excretion are higher toward the end of the experiments, when the cachexia is extreme, and in others they are lower. The concentration of cholesterol in the bile of the dog

83. Gardner, J. A., and Gainsborough, H.: Blood Cholesterol Studies in Biliary and Hepatic Disease, Quart. J. Med. **23**:465, 1930.

84. Garside, E.: Effect of Complete Biliary Fistula on Blood Cholesterol, Proc. Soc. Exper. Biol. & Med. **28**:336, 1930.

is low, usually averaging under 10 mg. per hundred cubic centimeters. In a few of our specimens much higher concentrations were found. These were clearly due to partial obstruction of the tube, allowing the bile to lie for periods in the gallbladder and to undergo concentration. That this is the correct explanation is shown not only by the finding of such obstructions but by the fact that during these periods the total daily excretion of cholesterol in the bile did not increase.

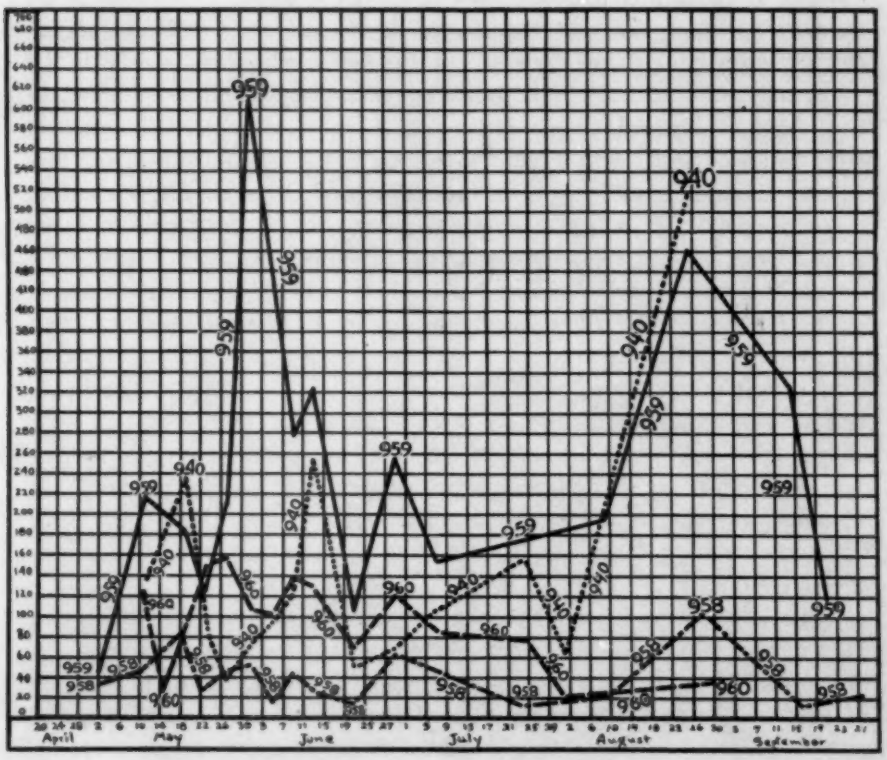

Fig. 8.—Graph showing the bile cholesterol curves of the dogs as given in tables 1 to 4. The dotted line represents dog 940, the dot and dash line dog 958, the solid line dog 959, and the dash line dog 960.

The evidence from these data is distinctly against cholesterol starvation. If it is then assumed that the cholesterol is exogenous (see comment under "The Sterol Balance"), one feels entitled to assume that it must be absorbed from the gastro-intestinal tract, and one is led to wonder why irradiated ergosterol should not be absorbed equally well, as it is decidedly more absorbable than ordinary sterols of animal origin.

RELATIONS TO PREGNANCY

One of the dogs (no. 959) had a litter of seven premature pups on the seventeenth day after the experiment began, and an unusual opportunity was thus offered to study the much disputed question as to the relation of pregnancy to cholesterol metabolism. The much greater incidence of disease of the gall tract in women and its close association with the puerperium have long been known. More recently

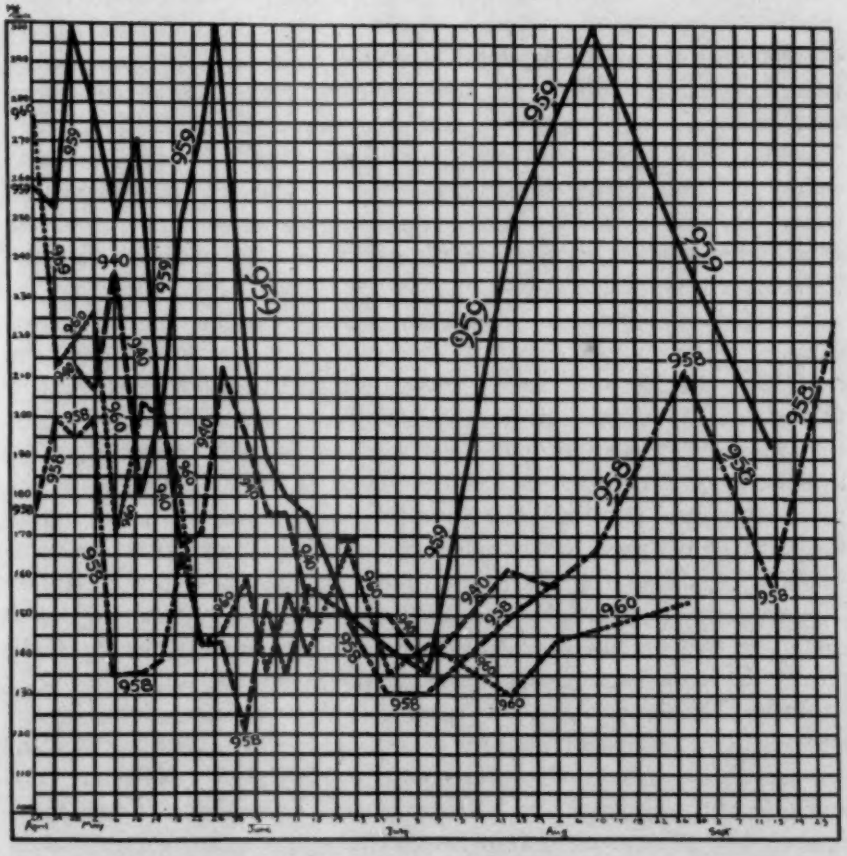

Fig. 9.—Graph showing the blood cholesterol curves of the dogs as given in tables 1 to 4. The dash line indicates dog 940, the dot and dash dog 958, the solid line dog 959, and the dotted line dog 960.

the association of pregnancy with hypercholesteremia appeared to complete the evidence, and the attractive theory was offered that gallstones are caused by an overflow of cholesterol into the bile, with consequent crystallization of the supersaturated solution.[85] However, as has been

85. McNee, J. W.: Zur Frage des Cholesteringehalts der Galle während der Schwangerschaft, Deutsche med. Wchnschr. **39**:994, 1913.

pointed out by Andrews, Schoenheimer and Hrdina in recent papers,[72] there is no proof that high blood cholesterol induces high bile cholesterol, and it has even been suggested by some that the mere fact that the blood cholesterol is high is indicative that the usual amounts are not excreted in the bile.[86] Others have shown that in the case of lipoid nephrosis, in which the blood cholesterol is extremely high, the bile contains normal percentages. Pribram,[87] however, reported evidence that in the later stages of pregnancy and during the succeeding months the cholesterol in the bile is markedly increased. His studies were based on analyses of material aspirated from the duodenum, which one must realize is mixed with intestinal secretions which have a high sterol content, considerably higher, in fact, than that of the bile.

With these points in view the findings on this animal are interesting (table 4). In the first place it is clear that there was no change in the blood cholesterol and that it lay in the same range as in the other three animals throughout the experiment. This is a distinctly different picture from that found in the human being, in whom the work of many observers shows that often there are at this period changes amounting to over 100 per cent. On the other hand, the changes in the bile were very striking. The average cholesterol content of the bile of the other three animals was 11 per cent, while that of the animal who went through the pregnancy was 25.7 per cent. The average amount excreted daily by the controls was 18.5 mg. while the pregnant animal excreted 42.1 per cent daily. The total excretion of the controls averaged 1,359 mg. while that of the pregnant animal was 4,229. These figures would be even more striking if the period studied included only the month before and the month after labor. It appears, therefore, that the cholesterol in the bile is increased at least threefold during the latter part of pregnancy and the month succeeding it.

In the dog the period of gestation is twelve weeks. Judging by the size and development of the fetuses they were about 8 weeks old, i. e., one month premature. The litter of seven weighed 1,960 Gm. (not including amniotic fluid and placenta, which were lost). From these fetuses 3.46 Gm. of cholesterol was extracted, a figure corresponding to about the normal percentage in blood. From table 4 it can be seen that the rise in bile cholesterol began at about the middle of the pregnancy and lasted for an equal period after delivery. Thus, applied to the human being, these figures should be multiplied by 3, the ratio of the two periods of gestation.

86. Gainsborough, H.: A Study of So-Called Lipoid Nephrosis, Quart. J. Med. **23**:101, 1930. Fox, F. W.: The Composition of Human Bile and Its Bearing upon Sterol Metabolism, ibid. **21**:107, 1927.

87. Pribram, E. C.: Zur Frage des Cholesterinstoffwechsels während der Schwangerschaft und im Wochenbelt, Arch. f. Gynäk. **120**:90, 1923.

On the other hand, there was no corresponding increase in the bile secreted, nor was there any rise in the bile acids. The bile acids of the pregnant dog averaged 266 mg. per hundred cubic centimeters, while three other dogs showed bile acid averaging 268, 346 and 453 mg., respectively. Thus, if anything, the level of the bile acids was lower although still easily within the limits of normal fluctuations. As a consequence there was an extended period in which the bile acid-cholesterol ratio was far below the critical point of 13. It has been previously reported by Andrews, Schoenheimer and Hrdina [73] that it took about 13 molecules of bile acids to hold 1 molecule of cholesterol in solution, and that if the ratio of the two was less than that figure, precipitation of the cholesterol was imminent. Unfortunately this bile was not examined for crystals before it was preserved in alcohol, as the chemical determinations were not made until after the conclusion of the experiment. These are the only figures that have come to our attention in which bile definitely supersaturated was secreted by the liver, as previous attempts to study this problem in dogs by variations in diet, etc., had always shown that such a condition was due to the action of the gallbladder.[20]

The effects of pregnancy on the other observations were nil. The blood calcium, blood fats and general progress of the cachexia were unchanged. One other point, however, is worth noting. Immediately after the litter was born a moderate degree of anemia developed, possibly due to hemorrhage at parturition. Two days after delivery the red blood cell count was 3,240,000 and the hemoglobin content 70 per cent. Within five days the red cell count had gone up to 5,160,000 and four days later to 5,720,000. There was no such prompt regeneration of the hemoglobin. This seems a striking example of the ability of the dog with a biliary fistula to regenerate blood, even in the absence of any specific adjuvant, and has direct bearing on the problem of anemia previously discussed.

BILE SALTS

The output of bile salts of our dogs was considerably lower than that usually reported for animals which were well fed throughout the experiment. Whipple and his associates [88] showed that a dog kept in good condition by bile, salmon bread, etc., will put out from 30 to 40 mg. of bile salts per kilogram of body weight per day under fasting conditions. This they assumed to be the "endogenous" bile salts, i. e., those derived from the breakdown of body proteins. They stated that

88. (*a*) Smith, H. P.; Groth, A. H., and Whipple, G. H.: Bile Salt Metabolism: I. Control Diets, Methods and Fasting Output, J. Biol. Chem. **80**:659, 1928. (*b*) Smith, H. P., and Whipple, G. H.: Salt Metabolism: II. Influence of Meat and Meat Extractives, Liver and Kidney, Egg Yolk and Yeast in Diet, ibid. **80**: 671, 1928.

any further secretion of bile salts is due to conversion of food into bile salts (the protein fraction, according to them). Whipple and his co-workers showed that the addition of fresh meat (liver, kidney or muscle) was the most potent in increasing the output of bile salts. On such diets the dogs excreted from 200 to 300 mg. per kilogram per day. Considerably less effective was egg or milk protein, while on diets of pancreas and fish (including the salmon bread) the daily excretion usually ran about 100 mg. per kilogram per day. Addition of carbohydrate had little or no influence on the output of bile acids, and on a purely carbohydrate diet the excretion stayed about the fasting level. Under these conditions the bile was highly colored, sticky and thin.

These findings in dogs with adjuvant feedings are strikingly different from those in our animals in which the deprivation of bile was total and a progressive emaciation was taking place. The average dog put out but 309 mg. of bile acids per hundred cubic centimeters of bile, although the figures for the individual dogs at various times varied as much as 1,000 per cent. These huge unexplainable fluctuations are a commonplace finding in all studies on bile and necessitate prolonged averages in order that definite interpretations of any given phenomenon may be made. This average is only about from one half to one third of the normal content. If measured as amounts excreted per day the average is 456 mg. per dog per day, a figure equally low. Most of Whipple's results are expressed as milligrams per kilogram per day, and the average of our entire series was 34.4 mg. per kilogram per day. This lies within the fasting range or the range of "endogenous" bile salts, as reported by Whipple and his co-workers, and makes it clear that there is a much greater fall in the bile acid content of the bile than in its volume or in any other of its constituents. Here again we find the wide (tenfold) daily variations, but there is a very clear tendency for each dog to run on its own individual level. This has also been commented on by Whipple.

It is interesting, however, to note that there was no progressive fall in the acids of the bile as the emaciation progressed (tables 1 to 4). The values calculated in the early stages are comparable to those calculated later. Even in the terminal stages two of the dogs had higher concentrations of bile acids and a higher output of bile acids per kilogram per day than immediately after the operation. This is clearly indicative of the fact that there is no lack of this molecule in the body, and that it is impossible to assign lack of bile acids to a prominent place in the etiology of biliary cachexia.

It has been stated by some that administration of viosterol would increase the acids in the bile.[66] This was tried on two of our animals in the terminal stages (last month). One of these dogs had the highest

elevation of bile salts during the entire period, and the other showed the lowest percentage of bile acids. In fact, this dog was the only one in which a profound terminal drop occurred.

The bile salt-cholesterol ratio as discussed ran, except in the pregnant dog, in the range previously reported by us for dogs, i. e., from 30 to 70. This is considerably higher than that found in man, who usually has a bile salt-cholesterol ratio of from 20 to 40.[89] Thus it seems suggestive that when there is a disturbance in the metabolism of one constituent because of the biliary fistula the other is affected in about the same degree. The apparent excretion of one in the same ratio as the other suggests that there is a common origin, and that the excretion of the two is in some way correlated.

THE STEROL BALANCE

The origins of the sterols in the body have been the source of considerable discussion. Any consideration of sterols must include with them the bile acids, the chemical constitution of which is so similar in spite of the utterly different properties. A consideration of the accompanying illustration of the structural formulas of representatives of the two groups makes it clear that the relationship is a close one. It might be expressed by saying that bile acids are the corresponding fatty acids of the sterol monohydric alcohols (although this is not a strict relationship). Furthermore, it seems that, as a catabolic phenomenon, the bile acids might be expected to be derived from the cholesterols by some process of oxidation. This possibility is further supported by the fact that while no bile acids are ingested in the ordinary course of events, most diets contain an abundance of sterols.

While the intricacies of sterol metabolism cannot be discussed here, a few salient points may be brought out. One often wonders why the term "sterol metabolism" is used when nothing is known of any changes that occur in the molecule after absorption, except for the finding of di-hydrocholesterol in the stools after ingestion of other sterols. No products of the oxidation of sterols have ever been recognized and no substances found which may be looked on as building stones in its synthesis. From the series of studies of Schoenheimer,[90] it is clear that plant sterols are totally unabsorbable from the mammalian gastrointestinal tract. However, if they are irradiated (as ergosterol), rapid absorption takes place. Ingested sterols of animal origin may be

89. Andrews, Schoenheimer and Hrdina.[73] Neuman, C. E.: Beiträge zum Studium der Gallenniederschläge und Gallensteinbildung, Beitr. z. path. Anat. u. z. allg. Path. **84**:187, 1931. Ravdin, I. S.; Riegel, C.; Johnston, C. G., and Morrison, P. J.: Studies in Biliary Tract Disease, J. A. M. A. **103**:1504 (Nov. 17) 1934.

90. Schoenheimer, R.: Newer Contributions to Sterol Metabolism, Science **74**:579, 1931.

readily absorbed. Evidence of synthesis of sterols in the body on any scale proportionate to the amounts daily excreted is totally lacking, but such a process on a very small scale cannot be denied. How important these small amounts may be is clear from a consideration of the fat-soluble vitamins and the profound physiologic events dependent on the presence of infinitesimal amounts of them. For a more complete discussion of these phenomena reference must be made to the elaborate studies of Windaus and of Wieland. Suffice it to say that no one has ever isolated from protein carbohydrate or fat any substance which in the least resembles the cholic acid radical fundamental to this group. How the plants manufacture sterols is not clear except for the undoubted fact that the yeasts build it out of carbohydrates. The reports of Whipple and his associates on the influence of carbohydrate in the decreasing of bile salts in the bile may have a bearing on this subject.

On the other hand, Smith and Whipple [85b] showed that ingestion of protein increases the acids in the bile and attributed this to an origin

TABLE 8.—*Data on the Total Sterol Balance in Four Dogs for from Four and One-Half to Five Months Each*

Intake	Output		
	Bile acids (bile)	235,304	
	Cholesterol (bile)	7,834	
	Cholesterol (feces)	7,009	
	Correction for about 25 per cent loss of feces	1,752	(estimate)
Total (food) 252,570 mg.	Total	251,999	

of the sterol molecule from the products of protein disintegration, assigning to the animal body an ability to synthesize these pyrrol ring products. It seems more logical to us to assume that the reason ingestion of protein increases the acids in the bile is that they are combined with either taurine or amino-acetic acid and that this is a method of eliminating these radicals.

In view of these facts it is interesting to study the sterol balance in biliary cachexia. Unfortunately our balance is not complete on account of the loss of stools, but a general idea may be arrived at and this loss allowed for, especially as the figure appears negligible in comparison with other far greater ones in the table (table 8). Allowance must also be made for the great inaccuracy of colorimetric methods of analysis as discussed. However, the very large number of estimations tend to balance themselves and at least partially to eliminate the error, and for this reason the average results should be best for study.

It can be seen that about 65 Gm. of sterol was ingested by our dogs in the experimental periods of from four to five months. Practically all the sterol is absorbable, as the amounts of sitosterol in bread are very

small and the sterols are mostly derived from the lard used in its manufacture. In this period, there were excreted in the bile about 2 Gm. and in the stools about the same amount, which should probably be doubled or tripled to allow for losses. This is especially true if one recalls Sperry's [91] experiments indicating that the amount of cholesterol in the stools is increased in the presence of a biliary fistula on account of incomplete absorption. Furthermore, our estimations of cholesterol were made by a colorimetric method which did not show the coprosterol which makes up much of the fecal lipoids. Against this, then, one may balance the loss of bile acids to the extent of about 59 Gm., which comes remarkably close to the establishment of a balance. One is tempted to assume that this amount of ingested cholesterol has been converted into bile acids.

If this is true the direct implication is that in the presence of biliary fistula at least the body does not synthesize sterol, neither cholesterol nor bile acids. The importance of this may not be very great. If the synthesis of sterols ceases, it is clear that the metabolism of this molecule is at a standstill. Considerable evidence is at hand [83] that the form of cholesterol and other absorbable sterols is not unchanged within the body. The conversion of the inactive ergosterol into the active form by sunlight is simply a change in isomerism, and many observers believe that comparable changes in the body sterols take place, and that the cholesterols found in the blood, bile, cell walls, etc., are not by any means identical optically, even if they are chemically, which in turn is uncertain. Even the transport of such substances within the body is difficult to understand in view of their extreme insolubility not only in water but in most body fluids. In bile they are held in solution, as Andrews, Schoenheimer and Hrdina [73] have shown, in a chemical combination with the bile salts. In the blood protein is probably the carrier. (Cholesterol is insoluble in blood and a chemical combination appears necessary.) Recent studies by Gardner and Fox,[92] Thannhauser and Schaber,[93] Beumer and Lehmann [94] and Randles and Knudson [95] showed

91. Sperry, W. M.: Lipid Excretion: IV. A Study of the Relationship of Bile to the Fecal Lipids with Special Reference to Certain Problems of Sterol Metabolism, J. Biol. Chem. **71**: 351, 1927.

92. Gardner, J. A., and Fox, F. W.: On the Origin and Destiny of Cholesterol in the Animal Organism: XII. On the Excretion of Sterols in Man, Proc. Roy. Soc. London, s.B. **92**:358, 1921. Fox, F. W.: The Origin and Destiny of Cholesterol in the Animal Body: XIV. The Cholesterol Metabolism in Normal Breast Fed Infants, ibid. **98**:76, 1925.

93. Thannhauser, S. J., and Schaber, H.: Kann der tierische Organismus Cholesterin synthetisieren? Ztschr. f. physiol. Chem. **127**:278, 1923.

94. Beumer, H., and Lehmann, F.: Ueber die Cholesterinbildung im Tierkörper, Ztschr. f. d. ges. exper. Med. **37**:274, 1923.

95. Randles, F. S., and Knudson, A.: Studies on Cholesterol: I. Synthesis of Cholesterol in the Animal Body, J. Biol. Chem. **66**:459, 1925.

beyond doubt that cholesterol may be synthesized by the mammalian organism. If, then, our studies of balance appear to indicate that sufficient sterols have been ingested to account for all the excretion in the case of a biliary fistula, the suggestion may be made that in this condition the synthesis of sterols ceases as the results are far different from those in the normal person.

If, then, the sterol metabolism is at a standstill, except for the suggested oxidation of cholesterol into bile salts, a readily soluble and excretable substance, it seems that we have at hand a rational explanation of the close similarity of the manifestations of acholic cachexia and avitaminosis. It also explains why in the total absence of bile from the stools some observers have reported benefit from viosterol and others not, and why the ingestion or even injection of viosterol into the dogs in the present study was of no avail, there being no means to transport or use it even when injected.

The disturbances or total interruption of the enterohepatic circulation of bile salts in jaundice is tolerated far better than biliary drainage, and, according to this assumption, it should be.

SUMMARY

A simple method of producing biliary fistula is described. By using this method we have had dogs survive considerably longer than they have after the use of any method previously reported on without adjuvant administration of bile, bile salts, liver, salmon bread, etc.

Anemia, osteoporosis or gastroduodenal ulceration did not develop.

The dogs did not manifest any lack of cholesterol or of bile salts in the body.

Their lives were not prolonged by the administration of vitamin D subcutaneously.

They did not exhibit "fat starvation."

Suggestive evidence is brought out that in the presence of a biliary fistula the bile salts are derived from the ingested cholesterol.

CONCLUSION

Acholic cachexia is not due to the absence of bile from the intestinal tract with consequent inability to absorb any specific food or vitamin. It is due to a disordered internal metabolism of sterols which inhibits proper utilization of them.

MALIGNANT DEGENERATION OF A BENIGN BONE CYST?

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The following case is reported for several reasons: First, as far as we could ascertain, a malignant change in a benign bone cyst has never been reported in the world literature. Second, a benign bone cyst in a child before it has begun to walk is a rarity. Third, team-work between surgeon, pathologist and roentgenologist and also between surgeon and surgeon is a necessity in developing the complete history and progress of an individual case.

REPORT OF A CASE

History.—I. M., aged 9 years, was referred to the clinic of Dr. Pusitz on Dec. 18, 1934, by Dr. Brethauer of Alta Vista, Kan., with the essential complaint of pain and swelling in the upper part of the right leg.

The history was that about three months before, while playing with other children in school, she was kicked on her leg. She did not have any immediate trouble; so the incident was forgotten. Shortly after this, however, she began to complain of slight pain, especially after being on her feet any length of time. In fact, the pain was present only when she walked. Rest gave relief. There was no pain during the night, and she slept well. The weather had no definite effect on the condition. About one month before she came to the clinic, she was seen by her family physician, who detected some swelling in the upper part of the right leg. This had not increased much in size. Whereas formerly she had always been a rather active child, she seemed to have lost her "pep". There had been no chills or fever. During the last week or so the tumor had become perceptibly warm. Because it was believed that she possibly had an infection of the bone, she was referred to the orthopedic clinic at Topeka.

She had had the ordinary diseases of childhood. At the age of 9 months, when she was beginning to walk, she slipped on a wet floor and hurt her leg. She complained of pain, but there was no swelling at the time. There was some slight deformity. The family physician told her parents that there might be a crack in the bone. The pain later became a prominent symptom, especially after she had tried to walk for some time. Because the pain increased in severity, she was taken

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From the service of the Kansas Crippled Children's Commission.

to Dr. Van Horne, of Topeka, a general practitioner. He took roentgenograms and told her parents that she had a sarcoma. He prescribed roentgen ray treatments, which she received for over a year. She seemed to be getting worse; so she was finally taken to Dr. Francisco, at Kansas City. Roentgenograms were again taken, but the diagnosis was bone cyst. Simple immobilization was instituted, first with a cast and later with a brace. About four and one-half years before the onset of the present illness she was pronounced cured, and the brace was discarded. She had no further trouble until the present illness. During this interval she was normal and active.

No important details were elicited in the family history of this patient. The parents were approximately 30 years of age when the child was born. Under the functional inquiry, it was noted that the patient was somewhat listless, drowsy and inclined to be "stupid" and that this was of recent development. No other points of any consequence were brought forth.

Examination.—Physical examination revealed a fairly well developed girl, who was not acutely ill. She did not complain of pain directly. No deformities of the head were noticed; no tenderness was present over the sinus regions; no rash was present over the face or neck. The conjunctivae were slightly pale; the scleras were normal; the muscles of the eyes were normal. The pupils were round and equal and reacted to light and in accommodation. Examination of the ears and mouth did not reveal any pathologic condition, nor did that of the neck or chest. The heart and lungs were perfectly normal. Examination of the abdomen also failed to reveal any pathologic condition.

There was a peculiar, rather fusiform swelling of the right leg, from just below the knee to the middle third of the leg. There was definite but not severe tenderness to pressure in the region, the point of maximum tenderness being a little below the metaphysis. Swelling and tenderness were most prominent over the anteromedial aspect. The mass was not particularly warm but was perceptibly warmer than the other areas of the leg. It was not hard, yet not fluctuant or cystic. It was not soft, but rather of a semisoft consistency.

Examination of the urine revealed no definite pathologic findings. The examination of the blood showed 81 per cent hemoglobin, 5,730,000 red cells, 7,500 white cells and a normal differential count. The Wassermann reaction was negative, as was the Kahn reaction.

Anteroposterior and lateral roentgenograms of the leg showed an extensive process involving over half of the shaft of the right tibia. There was a peculiar woolly appearance of the bone as a whole. There was erosion of the tibia on the anteromedial aspect of the upper part of the shaft, just below the metaphysis. There was evidence of periosteal reaction, in certain areas a sunray effect could be made out, as if spicules were laid down at right angles to the line of bone.

The clinical diagnosis made by the orthopedist was osteogenic sarcoma of the right tibia. The roentgenologist, however, diagnosed the condition as low grade chronic osteomyelitis. The parents were advised of the discrepancy in the views of the orthopedist and roentgenologist and were urged to accept exploration. A conjoint meeting of the orthopedist, the roentgenologist and the pathologist was arranged to occur in the operating room the next day.

On Dec. 20, 1934, a simple exploration was performed. Macroscopically the tissues resembled sarcomatous tissue rather than granulation (or cystic tissue). The roentgenologist stated that if the clinical and pathologic diagnosis was osteogenic sarcoma, the roentgenogram could be well interpreted as showing osteogenic sarcoma. A rapid frozen section was made by the pathologist (Dr. J. L. Lattimore), who made a diagnosis of osteogenic sarcoma.

As an unquestioned diagnosis was desired, and because roentgenograms of the lungs were desired by the orthopedist, it was decided to do a simple biopsy for the present and to amputate later. Since the patient had been under treatment by Dr. Francisco, he was called into consultation.

The history of the case had not been given as clearly as it has been presented in this outline, but with the additions made by Dr. Francisco, the complete history was available. His impression was that the tumor resembled an osteogenic sarcoma, but he thought it well worth while to delay amputation so that Professor Wahl could make a pathologic study, since the tumor had been benign before. Also he would hesitate before calling it malignant since he could not recall any case of malignant change in a benign bone cyst.

The reports from Professor H. R. Wahl, of the University of Kansas, Dr. Michele Gerundo, of the Topeka State Hospital at Topeka, Kan., and Dr. J. L. Lattimore, pathologist, were unanimous in pronouncing the section that of an osteochondrosarcoma.

Fig. 1.—Various views of the macroscopic specimen carefully dissected clean from the overlying tissue. From right to left, a medial view, a posterior view, a lateral view and a view of longitudinal sections, the section being made anteroposteriorly through the entire specimen.

The final diagnosis was therefore osteogenic sarcoma, and immediate amputation to be followed by irradiation was advised. The amputation was performed in the upper part of the thigh at the junction of the upper with the middle third, leaving just enough stump to control an artificial leg. The patient did exceptionally well after the amputation and has made a remarkable personal change. She received her first course of roentgen therapy and is to return for further irradiation under the supervision of the radiologist.

Macroscopic Examination.—The gross specimen was dissected out carefully after the amputation. A tumor was found involving the upper half of the tibia, extending all around the bone, but most apparent on the anteromedial aspect. The

pathologist stated that grossly the tumor was of an irregular, fusiform shape and measured 18 cm. in total length and 8 cm. in width at its greatest diameter. It was covered by the deep or vaginal fascia, which apparently formed an uninterrupted thick capsule over the underlying tumor. On the anterior aspect of the tumor there was a surgical incision about 5 cm. in length, and from the incision the neoplastic tissue was bulging out. In cutting the section, the knife encountered resistance, like that offered by cartilage. The surface of the section was grayish red, with a transparency similar to that of articular cartilage. No large vessels were present, and the tissue showed few hemorrhagic areas which could be attributed to vessels in the tumor. When the bone was cut longitudinally, the tumor was seen to extend from the metaphysis (which itself seemed to have been the site of an old fracture) downward to the segment corresponding grossly to the

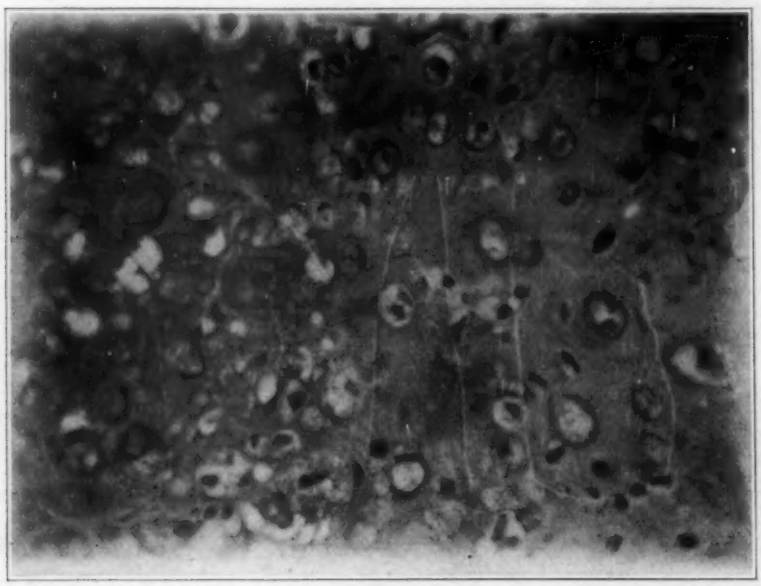

Fig. 2.—A high power photomicrograph of the section made from the tissue.

distal margin of the middle third of the bone. However, the medullary canal presented an extension of the tumor below the margin just described.

Although the periosteum seemed intact, particularly at the upper limit of the tumor, in the vicinity of the metaphysis, it seemed in direct continuity with the tumor tissue, and no separation of the two was possible in this locality. Also in the metaphyseal region, the bone was soft and rarefied, and in its central portion it could be scraped out with a knife. This was probably the zone which had given the impression of a bone cyst in the roentgenograms. Figure 1 illustrates various views of the gross specimen, including a longitudinal section through it.

Microscopic Examination.—Under the high power of the microscope, the tumor tissue was found to be made up chiefly of large capsulated cells, which had the characteristics of hyaline cartilage cells. There was no uniformity in the size of the cells, so that in the same field one could see very large cells with rather large nuclei and small cells with pyknotic nuclei. Two nuclei were often observed in

one capsule. Around such zones there were numerous cells of the same type, but growing without capsules, and other cells which showed a transition toward the fibrous type of cell. In these areas blood vessels were absent. In other zones a mucous degeneration of tumor cells was present, which gave the tumor a pseudomyxomatous appearance. The stroma, formed by a dense fibrous tissue, which in some places was difficult to distinguish from the tumor tissue itself, contained few vessels and some occasional hemorrhagic areas. It seemed to originate from the fascia, the prolongations of which, penetrating into the tumor tissue itself, gave to it a coarse lobulated appearance. Many cells were observed in various stages of division, and numerous mitotic figures were noted. Figure 2 illustrates a section of the tumor tissue highly magnified.

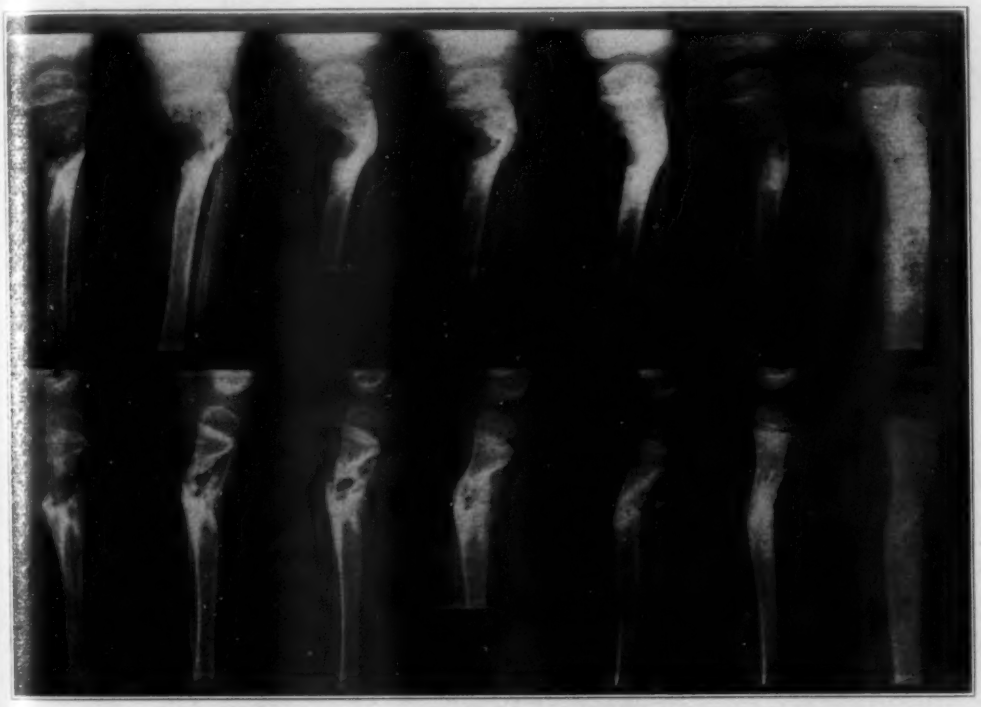

Fig. 3.—Comparison roentgenograms. In the upper row are the anteroposterior views in chronological order; in the lower row are the lateral views in chronological order.

The pathologic diagnosis was chondrosarcoma of the tibia originating from the metaphysis and extending to the diaphysis of the bone.

COMMENT

Although there are gaps in the history of this case, from the material collected from the family physician, the orthopedic surgeons and the parents (the general practitioner who took the first roentgenograms is dead), one can form a fairly good concept of the case as a whole.

It was noted that when the child was nine months old she slipped and fell, receiving a definite injury to the leg. Although the parents stated that there may have been some deformity at that time, this is questionable. Certainly, it was not deformity but pain which made them suspicious. Conservative treatment was tried for six months, but had no effect in lessening the pain. The child was therefore taken to Dr. Van Horne, at Topeka, when she was 15 months old. Roentgenograms at that time caused Dr. Van Horne to make a diagnosis of sarcoma, but his

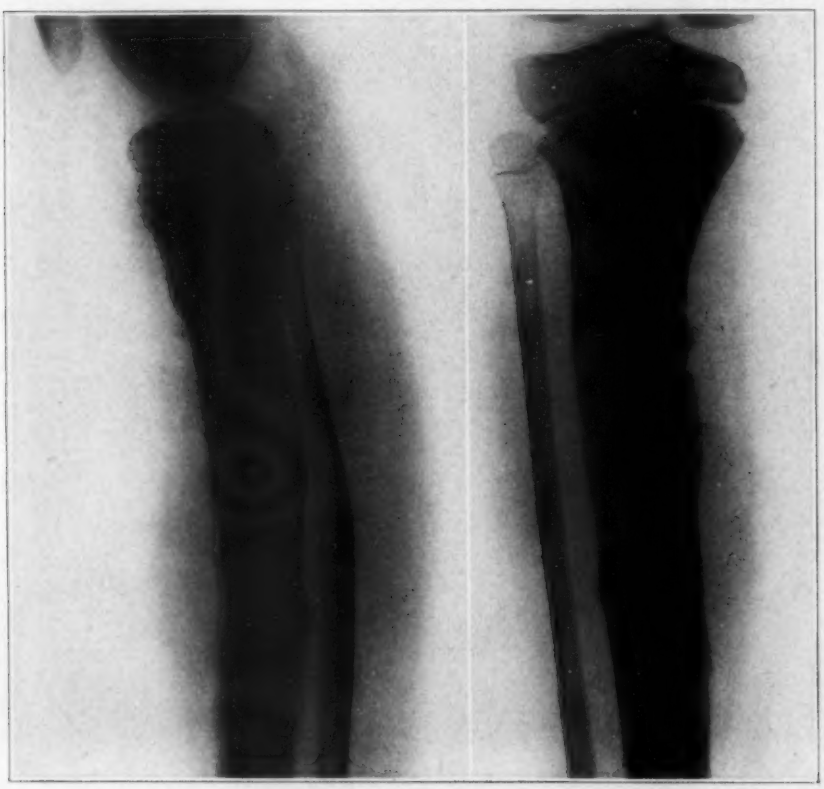

Fig. 4.—The final anteroposterior and lateral views, taken Dec. 19, 1934, when the tumor was diagnosed finally as an osteogenic sarcoma.

description to the parents was so characteristic ("the roentgenograms showed a soap-bubble effect in the upper end of the bone") that one does not doubt that he saw the same picture which Dr. Francisco found later. Roentgen ray treatment had no effect in controlling the condition, and again the symptom which caused them to seek further help was pain. No definite deformity was described at that time.

The child was approximately 3 years old when she was first seen by Dr. Francisco, and at that time no gross deformity was noted. There

is available the clinical history of the case from then until June 25, 1930. Dr. Francisco's series of roentgenograms, along with those taken in Topeka in December 1934, are illustrated in a comparative manner in figure 3.

Anteroposterior and lateral roentgenograms of the right tibia, taken on April 4, 1928, showed a multilocular cystic appearance of the upper end of the tibia. This began at or just below the metaphyseal end of the diaphysis and did not extend upward at all, so that the lesion did not affect the epiphyseal line. Areas of sclerosis were seen already lining some of the cystic cavities. The area of involvement extended downward for about one-third, or less, of the length of the shaft of the bone.

Similar views taken June 7, 1928, showed somewhat the same features, except that there seems to have been a mild pathologic fracture. The anterior wall of a large cystic area at the extreme anterior portion of the bone had been entirely absorbed. There was a sort of buckling in this region, causing an effect of hyperextension. The pathologic condition, however, was all below the epiphyseal line. There was much evidence of bone production, although the process did seem to have extended downward slightly. There was definite evidence of a pathologic fracture at that time. The parents also stated that from that time on they noted deformity in the upper part of the leg.

The roentgenograms taken on Sept. 22, 1928, showed still further condensation of bone, and those taken on Jan. 21, 1929, indicated a continuation of the process. The same may be said of those taken on Aug. 6, 1929. On June 25, 1930, the roentgenograms showed almost complete obliteration of the cystic cavities, with much condensation of the bone. It was at that time that the patient was discharged by Dr. Francisco as cured of the bone cyst. No further trouble was encountered until the present illness began.

DIFFERENTIAL DIAGNOSIS

If it were not for the malignant termination of the case, the only tenable diagnosis would be benign bone cyst. However, certain conditions must be thought of in the differential diagnosis, although in our opinion they can all be ruled out in favor of benign bone cyst.

Going back in the history, we found that a trauma of fairly severe nature had been sustained by the child. The question comes up as to whether or not she had a fracture at that time. Continental writers,[1] especially Italian, have spoken of a "softening of callus" which may result in areas of absorption so as to simulate the formation of cysts.

1. Jeanneney, G.: Les tumeurs des os, Paris, Masson & Cie, 1932. Uffreduzzi, O.: Trattato di patologica chirurgica generale e speciale, Torino, Unione tipografica editrice Torinese, 1933, vol. 1.

Callus is the result of a productive process. Clearly, along with this productive phenomenon there must be a retrogressive or absorptive change to give a cystic appearance. If this had been such a change, one would hardly expect the contour of the bone to be so regular, and certainly in the early stages there would have been evidence of a break. But it was not until June 7, 1928, that definite evidence of a pathologic fracture was seen. Even the parents cannot say certainly that there was definite deformity prior to this.

Benign chondroma may be considered only to be dismissed. In the first place, this tumor has an entirely different distribution than has a benign bone cyst. The growth is rare in persons under 20 years of age. The clinical symptoms are never severe. It is practically restricted to the small bones of the hands and feet and to the articular regions of the spine and the sternocostal joints. The roentgenogram shows a small translucent area of rarefaction. The cortical bone about the lesion is thinned and expanded. Pathologic fracture occurs in 10 per cent of the cases. Productive changes are rare.

The early stages of the condition in the case reported here certainly were not those of an osteogenic sarcoma, and this is proved by the progress of the case up to the discharge of the patient by Dr. Francisco in 1930.

There are two other possible conditions, namely, benign bone cyst and giant cell tumor. Bone cyst is a form of osteitis fibrosa [2] (although this statement should be modified) and is usually found in just the location described in the case in question. It is usually a solitary osteolytic tumor occurring in a patient under 20. In the early stages giant cells are noted in the bone tissues, pathologic overactivity of these cells, for some reason or other, resulting in the formation of the cyst. When the phase of bone destruction ceases, a stage of bone production ensues, especially about the periphery of the tumor. These two phases may overlap. The proliferation of the adjacent cortex and of the subperiosteal layer of osteogenic tissue (or the cambium of the periosteum) wall in the area of cystic activity. In multilocular cysts, the very walls of the subdivisions seem to have this power, as is evidenced in the roentgenograms (fig. 3). Especially is this process of proliferation enhanced when a pathologic fracture occurs. This seems to hasten the process to complete obliteration.

Although Geschickter [2] considered the benign bone cyst to be a variant of the giant cell tumor which has healed or is healing, there are certain distinct, fundamental clinical and radiologic differences:

2. Geschickter, C. F., and Copeland, M. M.: Tumors of the Bone, New York, American Journal of Cancer, 1931; Recurrent and So-Called Metastatic Giant Cell Tumor, Arch. Surg. **20**:713 (May) 1930.

First, a giant cell tumor is a solitary osteolytic tumor occurring in adults rather than in the younger groups. It is a progressive type of lesion and shows in the roentgenogram as a circumscribed, bone-destructive lesion occurring in the epiphysis. It usually shows a globular, trabeculated area of rarefaction, which is asymmetrical in position. It usually begins subcortically at one side of the epiphysis and gradually works its way toward the center, affecting the cancellous bone as it does so. Therefore, even though the histologic history of the benign bone cyst and that of the giant cell tumor may usually be the same, clinically and roentgenologically they are different. It is important to note that roentgen ray therapy has a remarkable effect on a giant cell tumor, whereas it does not have this marked effect on a benign bone cyst. Certainly the progress in this case would favor the diagnosis of benign bone cyst rather than one of giant cell tumor.

TREATMENT

It seems to us that the most important element in treatment is to enhance the proliferative acitivity. While roentgen ray therapy seems to act very well in certain cases of giant cell tumors, it seems too variable in its effect on bone cysts. Recently one of us had a chance to study the pathologic changes in a series of cases of bone cyst in four different clinics. While no statistical outline was made, it was noted that roentgen ray therapy did not give good results in treatment. In the cases in which pathologic fracture had occurred, the end-results were uniformly good, but the time factor was variable, as a rule being very much prolonged. In this case, of course, simple immobilization had been instituted. The best results, however, seemed to follow operation in which curettement, or curettement with application of a graft, was adopted. Here the results seemed very good, and the time required for complete obliteration of the cystic cavities was much less than with the other methods of treatment.

PROGNOSIS

The prognosis is usually excellent for complete obliteration of the cystic cavities. However, in certain cases years may be required before the terminal healed stage is reached. Recurrence is more frequent with conservative treatment than with surgical intervention. In the case reported, it is definitely known that the cyst was still present over four years after it was first observed. During this stage there were active young osteogenic cells claiming the picture. Can these cells assume malignant characteristics? Certainly in this case if the previous history had not been carefully and accurately obtained, the diagnosis of bone cyst might have been denied. Especially might this be true since the pathologic section showed the typical picture of chondrosarcoma. There

were no areas of cyst formation or of giant cells. Geschickter made the statement that there has never been reported a proved case of malignant degeneration following a benign bone cyst. He even denied the possibility of malignant degeneration following a giant cell tumor. He had at his disposal a wealth of material with all possible variations. It is difficult, therefore, to deny his statement and try to prove the contrary. Therefore, the case is left for future digestion and analysis, and the material will be placed at the disposal of the registry.

SUMMARY

A completely studied case is presented in which a chondrosarcoma arose at the site of a former benign bone cyst.

There are two rare features: First, the fact that the formation of cysts began when the patient first started to walk, and second, the malignant degeneration of the cysts.

CARCINOMA OF THE STOMACH FOLLOWING GASTRO-ENTEROSTOMY FOR PEPTIC ULCER

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The development of carcinoma of the stomach after a gastrojejunal anastomosis for chronic peptic ulcer is, on the whole, unusual. Its occurrence has been observed chiefly in certain cases of gastric ulcer for which gastro-enterostomy had been performed when, because of the great size, inaccessible location or extensive fixation of the lesion, its removal would have been an excessively difficult and hazardous undertaking. It is the consensus of most present-day writers in considering the life history of gastric ulcer that approximately 5 per cent of these benign ulcers will ultimately undergo malignant degeneration if they are not healable when treated by dietary or other nonsurgical measures. It therefore seems reasonable to assume that, likewise, gastric ulcers which fail to heal after an indirect type of operation, such as gastro-enterostomy, should show similar tendencies. Jean Varnier [1] estimated that carcinoma will ultimately develop in from 2 to 5 per cent of the cases in which gastro-enterostomy is performed for gastric ulcer. Some evidence on this score may be obtained from a study of the statistics from the Mayo Clinic.[2] There it has been found that in the cases of gastric ulcer dealt with by gastro-enterostomy alone, the death rate during the five year period following operation was two and one-half times as great as the death rate in a similar number of persons in the general population. Likewise, during the first year after operation, the death rate was 17 per cent in the group of patients with gastric ulcer in contrast to 5 per cent in the group of patients with duodenal ulcer treated by gastro-enterostomy.[3] It seems probable that malignant transformation is responsible, in part at least, for this higher death rate in the patients with gastric ulcer.

From the Department of Surgery, University of Michigan.

1. Varnier, Jean: Le cancer de l'estomac chez les ulcéreux gastriques opérés par gastro-entérostomie, Paris méd. **2**:93 (July 29) 1933.

2. Balfour, Donald C.: Results of Gastro-Enterostomy for Ulcer of the Duodenum and Stomach, Ann. Surg. **92**:558 (Oct.) 1930.

3. Horsley, J. Shelton, and Horsley, John S., Jr.: Surgical Diseases of the Stomach, in Graham, E. A.: Surgical Diagnosis, Philadelphia, W. B. Saunders Company, 1930, vol. 2, p. 553.

As the result of his clinical studies, Georg Wolfsohn [4] expressed the belief and presented some evidence to show that the incidence of carcinoma in patients with gastric ulcer not treated surgically is considerably higher than in those treated by simple gastro-enterostomy. He argued that even though an ulcer is not removed or even completely healed as the result of the operation, gastro-enterostomy, in some manner not clearly understood, affords a certain degree of protection against the later development of carcinoma.

With regard to gastro-enterostomy for duodenal ulcer, reported instances of gastric carcinoma developing after the operation are exceedingly rare. In a study of the end-results of gastro-enterostomy in 500 consecutive cases of duodenal ulcer, Balfour [2] found no instance of carcinoma developing subsequent to the operation as the cause of any of the late deaths in his series.

After an extensive search of the literature, I have been able to discover only five reports of carcinoma of the gastrojejunal stoma following operation for chronic duodenal ulcer. By far the most comprehensive case report and discussion of the matter appeared in 1932, in a paper by Singer.[5]

Singer, in discussing the relationship between gastro-enterostomy and the subsequent development of carcinoma of the stomach, presented a detailed report of a case of carcinoma of the gastrojejunal stoma occurring in a 64 year old man twelve years after a pylorectomy and posterior gastro-enterostomy for chronic duodenal ulcer. At the time of the original operation, the patient was found to have, in addition to the duodenal ulcer, chronic cholecystitis with extensive adhesions in the neighborhood. Accordingly, in addition to the pylorectomy and gastro-enterostomy, a cholecystectomy with lysis of adhesions was performed. There was complete relief from symptoms for one year following the operation, after which the patient began to suffer from a recurrence of his symptoms, necessitating a strict dietary regimen. In spite of this, the symptoms gradually increased, roentgen examinations repeatedly revealed a filling defect on the greater curvature in the distal third of the stomach, and the diagnosis of carcinoma of the gastrojejunal stoma was suggested by the roentgenologist. A laparotomy disclosed a soft, irregular mass in the region of the anastomasis. The gastro-enterostomy anastomosis was eliminated, the portion of the stomach containing the tumor was resected and the operation was concluded according to the Billroth II method. Death occurred two days later.

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4. Wolfsohn, Georg: Ueber Magenkarzinom nach Gastroenterostomien wegen Ulkus, Deutsche med. Wchnschr. **54**:1079 (June 29) 1928.

5. Singer, Harry A.: Carcinoma of the Gastrojejunal Stoma Following Operation for Peptic Ulcer, Arch. Int. Med. **49**:429 (March) 1932.

The tumor was described as polypoid and encircled approximately three fourths of the circumference of the stoma, its widest portion being near the side of the greater curvature. Microscopically it proved to be a carcinoma of multicentric origin, developing on the basis of multiple benign gastric polyps.

Singer stated that first a chronic gastritis had been initiated because of the irritation of the gastric mucosa by the intestinal secretions. This chronic gastritis was most severe in the neighborhood of the stoma. Multiple benign polyps then developed as the result of this inflammatory hyperplasia, and certain of these polyps ultimately underwent malignant degeneration. In this case there is convincing histologic evidence of the transition from inflammatory hyperplasia through benign to malignant neoplasia, and the gastro-enterostomy was, in all probability, an important etiologic factor in the development of the carcinoma.

Singer also referred to three similar cases in the literature: the case of Schwarz,[6] the one of Hurst and Stewart[7] and the one of Eichelter.[8] These reports have been verified by me, and one possible additional case has been noted.

In the case reported by Schwarz a patient who had had an anterior gastro-enterostomy for a pyloric ulcer was relieved from symptoms for about six years, after which vomiting and loss of weight occurred. A laparotomy showed a carcinoma of the gastro-enterostomy stoma producing great dilatation of the proximal jejunal loop, while the distal loop was collapsed. There were metastases in the regional lymph glands and on the peritoneum. A Braun anastomosis was performed, and rapid recovery followed.

Hurst and Stewart made reference to a carcinoma of the gastro-jejunal ring, but clinical notes and a detailed description of the tumor are lacking.

A man of 59 was operated on by Eichelter for general peritonitis. Three and one-half years before, he had had a partial gastrectomy for a penetrating ulcer. At the time of his operation, Eichelter found a nodular tumor at the site of the anastomosis, and there was great dilatation of the proximal loop with perforation of an acute ulcer of the duodenum. A duodenojejunostomy with jejunostomy was performed. Death occurred two days later. Necropsy disclosed a firm growth, which originated at the anastomosis and encroached on the

6. Schwarz, in discussion on Lengemann: Operationsbefunde an Gastroenterostomierten, Zentralbl. f. Chir. **53**:3000 (Nov. 20) 1926.

7. Hurst, A. F., and Stewart, M. J.: Gastric and Duodenal Ulcer, New York, Oxford University Press, 1929, p. 429.

8. Eichelter, G.: Spontanperforation des paralytisch erweiterten Duodenalschenkels 4 Jahre nach subtotaler Magenresektion wegen ulcus (Primäres Karzinom an der Anastomosenstelle), Deutsche Ztschr. f. Chir. **222**:106, 1930.

lumen. Microscopically it proved to be carcinoma, and there were metastases in the liver, esophagus and regional lymph nodes.

Beatson [9] reported the case of a 52 year old man who came under observation with the complaints of vomiting, diarrhea, epigastric pain and abdominal tumor. Eleven years previously a gastro-enterostomy had been performed for a "dilated stomach" (possibly due to a pyloric ulcer). He was well for eight or nine years, after which his health began to fail. A second laparotomy was performed, and a carcinomatous mass was found on the lesser curvature, stretching down the posterior wall and involving the new gastro-enterostomy opening. Owing to the presence of metastases, nothing was done. He died twelve years after the first operation. Necropsy showed a firm mass occupying the pyloric portion of the stomach. The gastro-enterostomy stoma was surrounded by the ulcerated new growth, with obstruction of the efferent jejunal loop. Microscopically the lesion proved to be an adenocarcinoma of the stomach.

Beatson offered two possible interpretations of the findings in this case: The first assumed that the original gastro-enterostomy was done for pyloric obstruction due to a gastric ulcer near the pylorus and that subsequently this ulcer had become malignant and in the course of its growth had extended into the gastro-enterostomy opening. His second explanation was that the malignant lesion had started in the wall of the gastro-enterostomy wound on the gastric side and by extension had involved the pylorus. The first view seems the more tenable.

To the cases just cited I am able to add a verified case of carcinoma of the gastrojejunal stoma occurring in a man of 49 seven years after a von Eiselsberg exclusion operation for chronic duodenal ulcer.

REPORT OF A CASE

History.—Mr. T. T., a Czecho-Slovakian factory worker aged 42, was admitted to the University Hospital on Aug. 8, 1927, with the complaint of "pain in the stomach." The family history was excellent, there being no history of malignant disease. The past history of the patient was essentially unimportant. The patient had enjoyed good health until about one and one-half years before admission to the hospital, when he began to be troubled with severe epigastric pain, which became progressively worse. The pain usually started in the right lower quadrant and radiated to the right upper quadrant and over to the midline. Frequently it began in the epigastrium and radiated to the right lower quadrant. The pain came on from one to one and one-half hours after meals and was often followed by vomiting, which afforded some relief. He was unable to say whether food or soda would relieve the pain. There had been a loss of weight of 24 pounds (10.8 Kg.) during the preceding few months.

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9. Beatson, George T.: Carcinoma of the Stomach After Gastrojejunostomy, Brit. M. J. **1**:15 (Jan. 2) 1926.

Examination.—The positive physical findings were (1) poor nutrition, (2) dental caries with many missing teeth, and (3) moderate tenderness without muscle spasm in the right lower and the right upper quadrant.

The Kahn reaction of the blood was negative. Examination of the blood revealed a hemoglobin content of 80 per cent (Sahli) and a leukocyte count of 11,400. The urine was normal.

Roentgen studies on Aug. 8, 1927, showed (1) "a normal stomach and duodenum, and (2) nonvisualization of the gallbladder by the Graham test." On Aug. 13, 1927, roentgenograms showed a healthy chest. A tentative diagnosis of chronic cholecystitis was made, and it was thought that the symptoms were sufficiently severe to warrant operation.

Operation.—Operation was performed on Oct. 8, 1927, by Dr. Hugh Cabot. Ethylene and ether anesthesia was used. The gallbladder was found to be normal

Fig. 1.—Roentgenogram made on May 21, 1934, showing marked gastric retention and a filling defect in the lower portion of the stomach.

in all respects. The pylorus was involved in what appeared to be a chronic ulcer. This was dealt with by dividing the stomach just above the pylorus, thus disconnecting it from the duodenum. An end-to-side anastomosis was then performed between the stomach and the jejunum, a procedure which was thought to be a more satisfactory operation in this case than the usual posterior gastro-enterostomy, as the duodenum was still open. Before the end of the distal segment was closed, the noncrushing clamp was relaxed and the areas were examined, and the lesion was found to be entirely in the duodenum.

Postoperative Course.—The convalescence was uneventful. The result of a check-up roentgen examination made on Oct. 19, 1927, was reported as follows: "Postoperative examination of the upper part of the gastro-intestinal tract demonstrated the gastrojejunostomy stoma to be open and functioning well." The patient was discharged on Oct. 22, 1927, on a Mills IV diet.

Pathologic Report.—A lymph node removed from the region of the stomach was reported by Dr. A. S. Warthin as showing "chronic lymphadenitis, acute congestion and edema but no neoplasm."

Second Admission.—On May 18, 1934, the patient returned with the complaint of abdominal pain, vomiting, diarrhea, weakness and loss of weight.

He had remained well after his discharge from the hospital until the fall of 1933 (six years). During this time he had gained considerable weight, was able to work and had been entirely free from symptoms. He had adhered to the prescribed diet for several months and then began to eat without restriction. In the fall of 1933 diarrhea suddenly developed, the stools numbering from ten to twenty a day. In addition to this, for the three weeks before admission, there had been a dull aching epigastric pain accompanied by vomiting. The pain had

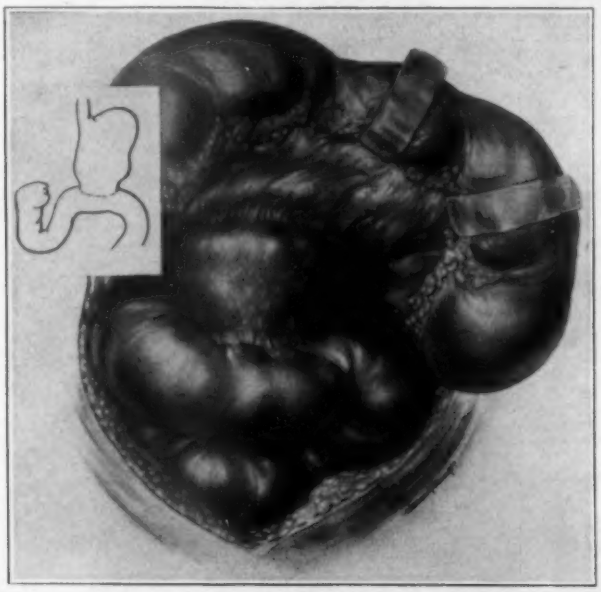

Fig. 2.—Sketch made at the time of the second operation, showing the carcinoma situated at the gastrojejunal ring. The carcinoma completely encircles the stoma and is limited to the gastric side of the junction, the jejunum remaining uninvolved. The insert shows diagrammatically the nature of the original operation performed in 1927.

been aggravated by food. Finally he had been able to tolerate only small quantities of milk and water. He had lost 29 pounds (13.1 Kg.) in weight since these symptoms had been present.

Examination.—There was evidence of considerable loss of weight, moderate emphysema and an abdominal tumor attached to the old scar left by an upper right rectus incision. The mass seemed to be about the size of a small orange and moved downward with respiration. It was hard and firm and felt somewhat nodular. In the left upper quadrant the outline of the distended stomach could be clearly made out. There was definite resonance on percussion over this area.

The Kahn reaction of the blood was negative. A blood count revealed: hemoglobin, 75 per cent (Sahli); erythrocytes, 4,550,000; leukocytes, 5,800. The

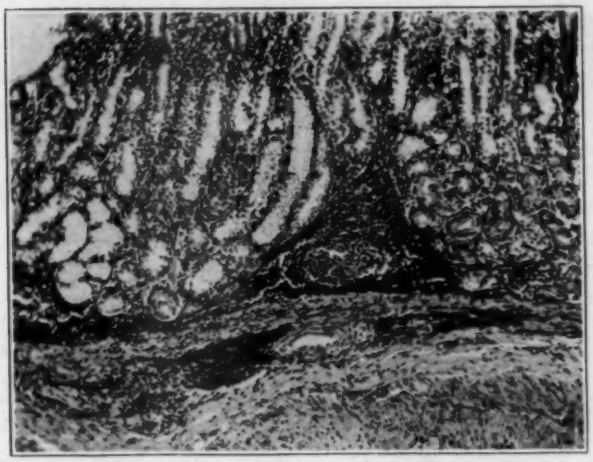

Fig. 3.—Photomicrograph (× 85) of the gastric mucosa near the gastroenterostomy stoma. The mucosa is thickened by an increase in size and number of the epithelial cells and by the heavy infiltration by lymphocytes and plasma cells. There are a marked increase in the formation of mucin and hyperplasia of the intrinsic lymphoid tissue.

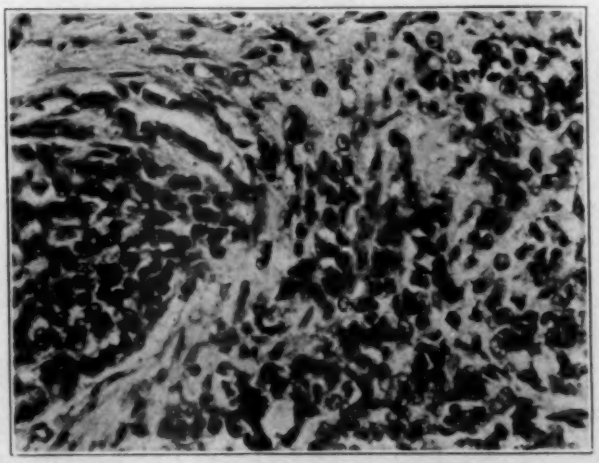

Fig. 4.—Photomicrograph (× 400) of the gastric wall near the gastroenterostomy stoma. Scirrhous carcinoma tissue infiltrates the muscle tissue and appears in the subserous connective tissue. Associated with the carcinoma is an active fibroblastic proliferation.

differential count showed: polymorphonuclears, 55 per cent; basophils, 1 per cent; eosinophils, 1 per cent; lymphocytes, 39 per cent; mononuclears, 4 per cent. The color index was 0.82. The red cells appeared normal. The platelets were normal in number. The urine was normal aside from a faint trace of albumin. The stool gave a positive reaction to the benzidine test but was otherwise normal. Examination of the gastric contents revealed no free hydrochloric acid after the injection of histamine.

The report of a roentgen examination on May 21, 1934 was: "There is marked gastric retention with a constant filling defect in the lower portion of the stomach, giving the impression of neoplasm in the distal third of the stomach causing gross obstruction" (fig. 1).

The clinical diagnosis was (1) marginal ulcer or (2) carcinoma of the stomach obstructing the gastro-enterostomy stoma. Operation was advised.

Operation.—Operation was performed on May 26, 1934 (H. K. R.). Tribromethanol in amylene hydrate and ether were used for anesthesia. The palpable mass was found to involve the distal portion of the stomach, the upper half of the stomach being essentially normal. The greater portion of the tumor lay behind the transverse colon and was intimately attached to the liver and the gallbladder (fig. 2). It was mobilized, and the gross appearance suggested a scirrhous carcinoma. It seemed to originate from the wall of the stomach and ended abruptly at the point where the stomach and jejunum had been joined at the former operation. It completely encircled the stoma and thereby produced considerable obstruction at the outlet of the stomach. There were no metastases, and the fixation to the liver and gallbladder was thought to be inflammatory. The lower portion of the stomach, including the entire mass, was resected and also the segment of the jejunum involved in the old anastomosis. An end-to-end anastomosis was then done between the ends of the jejunum, and the mouth of the remaining gastric pouch was reanastomosed to the side of the jejunum just distal to this end-to-end anastomosis. The stump of the duodenum was found buried in old adhesions. There was no evidence of abnormality at this point, and accordingly it was not disturbed.

Postoperative Course.—The convalescence was uneventful, and the patient was discharged from the hospital on June 12, 1934.

Pathologic Diagnosis.—The pathologic diagnosis given by Dr. J. C. Bugher was: "Advanced scirrhous carcinoma infiltrating entirely through the stomach wall, marked hyperplastic gastritis and subserosal carcinomatous infiltration. The portion of intestine shows chronic catarrhal inflammation with some hyperplasia of the mucosa. There is no carcinoma on this portion" (figs. 3 and 4).

Subsequent Course.—It has been impossible to follow the subsequent course in this case, as the patient has never returned to the clinic since his discharge, and letters to him have been returned unanswered.

COMMENT

This case seems similar in many respects to the one reported by Singer. As in Singer's case, well marked chronic hyperplastic gastritis with occasional areas of polypoid overgrowth was present, and this very possibly was the forerunner of the malignant neoplasm. It seems logical to assume that the chronic gastritis was due to the continued

chemical trauma to which the gastric mucosa was subjected by reason of the constant reflux of alkaline intestinal secretions from the jejunum.

In an organ such as the stomach in which malignant disease is prone to occur, it does not seem unreasonable to suppose that in the course of this inflammatory process the cells had exceeded the bounds of normal and orderly growth and progressed to the stage of blastomatous proliferation.

Of the late complications occurring at the stoma in cases of gastro-enterostomy performed for duodenal ulcer, an inflammatory lesion originating chiefly on the jejunal side of the anastomosis (jejunal ulcer) is the one most commonly encountered. Apparently, as a rule, the mucous membrane of the jejunum is more liable to injury as the result of the altered physiology and chemistry produced by the operation than is the lining membrane of the stomach. Moreover, the incidence of malignant degeneration in persons with jejunal ulcer is insignificant, in analogy with the well known rarity of carcinoma of the upper portions of the small bowel.

In the case herein reported and in the small number of similar cases found in the literature a reversal of this more usual course of events apparently took place following the gastro-enterostomy. Thus the major inflammatory changes occurred in the stomach, and perhaps from this hyperplastic inflammatory process carcinoma subsequently developed at the gastrojejunal ring, and obstructive symptoms finally developed as the growth seriously compromised the opening.

A point of some additional interest is the fact that just as in cases of carcinoma of the lower portions of the stomach the neoplasm is usually found to end abruptly at the pylorus and rarely invades the duodenum, so in this case of gastric cancer involving over one third of the stomach, the growth was limited entirely to the gastric side of the anastomosis. Although the lesion completely encircled the stoma, both grossly and microscopically, the jejunum was found to have successfully resisted invasion by cancer cells.

CHRONIC SUBDURAL HEMATOMA

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The study of chronic subdural hematoma may be divided chronologically into very definite periods. Prior to 1857 there were scattered records of observed cases of patients who were found at autopsy to have a collection of blood beneath the dura. In 1857 Virchow,[1] as a result of postmortem studies in a number of cases, introduced the term pachymeningitis haemorrhagica interna. Since in the cases studied by him there was no history of trauma, he thought that the underlying pathologic process was the organization of an inflammatory exudate. From 1857 until 1925 the lesion was studied extensively by many pathologists and neurologists, but with a few exceptions their chief interest was the underlying pathologic process rather than the treatment of the condition. A notable exception was an article by Trotter[2] published in 1914; in it four cases in which the condition was treated surgically were reported. Although very little of practical value has been added since, Trotter's contribution was generally overlooked until, in 1925, an excellent review of the literature and a report on twelve patients treated surgically was presented by Putnam and Cushing[3] in collaboration with other members of the Society of Neurological Surgeons. Of the twelve patients reported on eight recovered after operation for removal of the clot. This extremely valuable communication not only served to bring about a great revival of interest in a condition which is amenable to proper surgical treatment but also clarified to a great extent the confusion which had existed from the standpoint of the underlying pathologic process.

Putnam concluded that there were, in general, two classes of hemorrhagic subdural hematoma. The first he called the vascular type, and this is the lesion seen fairly frequently at autopsy on patients who have died of chronic alcoholism and of chronic wasting diseases. The histologic

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From the Neuro-Surgical Service of the Washington University School of Medicine, the Barnes Hospital and the St. Louis Children's Hospital.

1. Virchow, R.: Haematoma Durae Matris, Verhandl. d. phys.-med. Gesellsch. **7**:134, 1857.

2. Trotter, Wilfred: Subdural Hemorrhage of Traumatic Origin and Its Relation to Pachymeningitis Hemorrhagica Interna, Brit. J. Surg. **2**:271, 1914.

3. Putnam, Tracy J., and Cushing, Harvey: Chronic Subdural Hematoma, Arch. Surg. **11**:329 (Sept.) 1925.

picture in the membrane, according to Putnam, varies from the traumatic type in the size and appearance of the new-formed vessels in the wall of the sac which underlies the dura. These vessels, except for size, have the appearance of normal capillaries. They are frequently 40 microns or more in diameter.

The second type, which he called reactive or traumatic, is the one which concerns the surgeon. The gross appearance may be practically identical with that of the foregoing type, but the clinical behavior is very different. Putnam stated that hematoma of this type may be differentiated histologically from that of the first type but that the difference is so slight that the two may be easily confused. In the wall of the sac just beneath the dura are irregular blood-filled spaces lined with mesothelium. These are much larger than the giant capillaries, and the spaces frequently become confluent with each other. They anastomose with the normal capillaries seen in the wall of the sac.

It is with this reactive, or traumatic, type of subdural hematoma that this paper deals. I propose to show that: (1) The condition is more frequent than is commonly supposed; (2) proper treatment, when the condition is recognized sufficiently early, offers a good prognosis; (3) the symptomatology is vague, and the history of trauma may be so slight as to be entirely overlooked. In addition, the records of sixteen cases treated in this neurosurgical clinic will be given.

CLINICAL BEHAVIOR

Subdural hematoma may occur at any age and in either sex, but it is more frequent in men because of their greater exposure to injury. After an injury, which may be very trivial or relatively severe, there is an interval, which may vary from a few days to months or even a year or more, in which the patient is practically symptom-free. He then begins to present evidences of chronic progressive increasing intracranial pressure, and not infrequently the diagnosis of tumor of the brain is made. He may come to the surgeon while his general condition is still good, but all too frequently he arrives in a profoundly unconscious state and in the last stages of cerebral compression. The usual points in the history are headache, vomiting, gradual diminution in visual acuity, diplopia, convulsions, mental disturbances, etc. No one factor is common to all cases, and in spite of the fact that the location of the hematoma is fairly constant over the convex portion of the cerebral hemisphere, the findings on neurologic examination are extremely variable and frequently so confusing that in order to make the diagnosis it is necessary to resort to ventriculography [4] or to make trephine openings.

4. Dandy, Walter E.: Ventriculography Following the Injection of Air into the Cerebral Ventricles, Ann. Surg. **68**:5, 1918.

The most common factor occurring in the histories of patients with subdural hematoma is trauma. Not infrequently it is so trivial and occurs such a long time before that information in regard to it is not volunteered but has to be sought. This brings up the question of the mechanism by which these patients remain symptom-free for varying periods. This lapse of time between the trauma and the onset of symptoms has been called the latent interval. Recently it has been the subject of much speculation and some experimentation.

Trotter [2] concluded that the source of the hemorrhage was almost always one of the bridging veins running from the cortex across the subdural space into the superior longitudinal sinus. He thought that repeated small hemorrhages gradually increased the size of the hematoma until finally the limits of cerebral compression were reached. Putnam and Cushing [3] expressed the belief that this must be the correct explanation, and Keegan [5] cited as evidence of its truth a case in which at operation he found a small tear in the longitudinal sinus, from which there was bleeding only when the patient strained. From this he concluded that renewed bleeding was brought about by transitory rises in intracranial pressure. Leary [6] made postmortem studies on fifty patients with subdural hemorrhage and concluded that this explanation was correct.

Nevertheless, the theory has not been universally accepted, for in order to accept it one must conclude that bleeding into the subdural space violates practically all the rules for bleeding into the other tissue spaces of the body. Experimental investigation of the problem has been practically impossible, for no one has successfully produced typical subdural hematoma in experimental animals.[7] Spiller,[8] in 1899, succeeded in producing the typical membranes in dogs by hemorrhage from the superior longitudinal sinus, but there was not the fluid content that is seen in clinical cases.

McKenzie [9] suggested the possibility of an increase in size of the sac by a process of osmosis. Gardner,[10] in a recent article, said that the

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5. Keegan, J. J.: Chronic Subdural Hematoma: Etiology and Treatment, Arch. Surg. **27**:629 (Oct.) 1933.

6. Leary, Timothy: Subdural Hemorrhages, J. A. M. A. **103**:897 (Sept. 22) 1934.

7. Putnam, T. J., and Putnam, I. K.: The Experimental Study of Pachymeningitis Hemorrhagica, J. Nerv. & Ment. Dis. **65**:260, 1927.

8. Spiller, W. G., and McCarthy, D. J.: A Case of Internal Hemorrhagic Pachymeningitis in a Child of Nine Years, with Changes in the Nerve Cells, J. Nerv. & Ment. Dis. **26**:677, 1899.

9. McKenzie, K. G.: A Surgical and Clinical Study of Nine Cases of Chronic Subdural Hematoma, Canad. M. A. J. **26**:536, 1932.

10. Gardner, W. J.: Traumatic Subdural Hematoma, Arch. Neurol. & Psychiat. **27**:847 (April) 1932.

wall of the sac acts as a semipermeable membrane and that as the complex protein molecules of the blood disintegrate, fluid enters the sac, thus increasing the bulk of the lesion. He reported experimental evidence to support the theory, and Zollinger and Gross,[11] after observation on an intact membrane removed surgically, stated that this is true.

TREATMENT

Surgical intervention is the only treatment of any avail for subdural hematoma. In this clinic, the practice has been to make an osteoplastic flap and remove the liquefied portion of the clot and as much of the surrounding membrane as possible. However, Trotter[2] stated that mere evacuation through an opening in the temporal fossa would result in a cure. Recently, McKenzie[9] reached the conclusion that the osteoplastic flap is usually unnecessary and may be dangerous. He advocated removing the contents of the sac by suction through a small opening in the bone and subsequent drainage of the subdural space for forty-eight hours. Fleming and Jones[12] reported eight cases, with one death, in which two openings were made and the contents of the sac washed out. In their series of eight cases, the hematoma was bilateral in 50 per cent, so that they made bilateral openings for exploration in every case.

There have been two chief reasons why the method of osteoplastic flap has continued in use in this clinic. In the first place, drainage through a small opening has not always been successful (cases 4, 7 and 9), and secondly, it has been felt that it is wiser to remove the membrane. Horrax (quoted by McKenzie[9]) on one occasion reflected a flap three months after the contents of a hematoma had been sucked out and found that both the outer and the inner membrane had disappeared. However, one cannot be sure from this single observation that this is always the case.

It is certainly true that evacuation through small openings is a much less formidable procedure than the use of an osteoplastic flap. It is also true that the patient not infrequently comes in a state of coma (five of sixteen in the present series); and since of the six patients in this series who died, five were in coma, in the future the method of treatment may be modified by using small openings for the patients in a comatose state and a flap when the patient's condition is good.

The following cases will serve to emphasize the points of importance in the diagnosis and treatment of the condition.

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11. Zollinger, R., and Gross, R. E.: Traumatic Subdural Hematoma: An Explanation of the Late Onset of Pressure Symptoms, J. A. M. A. **103**:245 (July 28) 1934.

12. Fleming, H. W., and Jones, O. W.: Chronic Subdural Hematoma, Surg., Gynec. & Obst. **54**:81, 1932.

REPORT OF CASES

CASE 1.[13]—J. H. A., a Negro aged 58, entered the Barnes Hospital on Nov. 27, 1919. He was admitted to the medical service in a state of unconsciousness. Four months before he had been in an automobile accident and had been unconscious for twelve hours. What followed is not recorded, but a few days before admission to Barnes Hospital, he had been sent to a local hospital because of mental changes. He had been forgetful and irrational and had complained of dizziness. A lumbar puncture was made, after which he became much more stuporous, and the Cheyne-Stokes type of respiration developed. At the time of admission, he was unconscious and had bilateral choked disk, with hemorrhages in the right eye, pathologic toe signs on the left side and some spasticity of both arms. The left arm was not moved voluntarily.

A diagnosis of tumor of the frontal lobe on the right side, probably in the last stages of compression, was made. With the concurrence of Dr. Schwab, the patient was transferred to the neurosurgical service, and because of his precarious condition a subtemporal decompression on the right side was decided on. The dura pulsated but had a bluish appearance, and when it was incised the membrane of a subdural hematoma was encountered. A large amount of old fluid blood was evacuated. As much of the membrane as could be reached was removed, and the wound was closed with silk.

Following operation, the patient's state of unconsciousness became more profound. There was a rising blood pressure and a slowing pulse rate; hence the same night the wound was reopened. When the muscle sutures were removed, a large amount of old blood mixed with cerebrospinal fluid was evacuated. A rubber tissue drain was put in through the opened dura and the wound closed. The patient's condition gradually grew worse. He contracted pneumonia and died on November 30.

Autopsy was performed, and such marked compression of the right hemisphere was present that the right ventricle was practically obliterated. There was a small amount of subdural hematoma on the left side, but no bleeding around the operative site. There was definite bronchial pneumonia.

Comment.—This case illustrates a number of important points. In spite of the definite history of trauma, subdural hematoma as a diagnosis was not considered. There was marked aggravation of symptoms after lumbar puncture, and the puncture was undoubtedly a great factor in the cause of death. Although the apparently correct treatment was carried out, the patient did not improve after operation. In the discussion of the case by Putnam and Cushing,[3] it was said that in spite of the decompression the edema of the brain progressed to such an extent that the ventricle was almost obliterated by swelling. This is an erroneous conception. What actually happened is that when the hematoma was removed a large "dead space" was left. The ventricle on that side had been markedly compressed, and after operation the brain failed to expand, so that at autopsy the ventricle on that side was still compressed as it had been before operation. Just how to deal best with this dead space is still a problem, for in one other case the findings were similar (case 12).

13. This case is included in the study by Putnam and Cushing [3] as case 6.

CASE 2.—J. R., a white man aged 40, was admitted to the Barnes Hospital on April 7, 1924. There was no definite history of injury. For a month before admission he had had rather severe headache and intermittent diplopia. The diplopia at times was so pronounced that it was almost impossible for him to drive his car. For several days he had had difficulty in swallowing and a disturbance in speech, and recently there had been a drooping of the left eyelid. He was markedly emaciated, but careful search for tuberculosis revealed no focus. Neurologic examination showed bilateral choked disk, weakness on the left side of the face and pathologic toe signs on the right side.

The uncertainty of the localizing diagnosis made ventriculography necessary, and on April 23 ventriculography was attempted. There was a greenish membrane beneath the dura on the right side, and it was impossible to make an opening into the ventricle on that side. An opening was made on the left side, and about 12 cc. of bloody fluid was removed and replaced with air. Plates showed no air in the ventricular system.

On April 25 a subtemporal decompression was done on the right side, and the typical greenish-blue membrane of a subdural hematoma was found and removed.

The postoperative course was uneventful. At the time of his discharge on May 3, the patient was in good condition.

Comment.—It is interesting that in spite of recognizing the bluish-green color which is so typical of subdural hematoma, ventriculography was still considered necessary. This also shows that trauma may be so slight that it goes unnoticed.

CASE 3.—C. R., a white girl aged 4 years, referred by Dr. Paul C. Carson, of Wichita, Kan., was admitted to the Children's Hospital on March 20, 1927. There was a definite history of injury a year before admission, but there was not complete loss of consciousness. The patient had complained at intervals of headaches, which had recently become much more severe, and projectile vomiting had developed. She did not see as well with the right eye as with the left, but she was too young to be given tests for visual fields or visual acuity. Her head had always been rather large, but since the injury it had increased in size and measured 52 cm. There were bilateral choked disk and prominent veins on the forehead. A roentgenogram showed marked evidence of increased intracranial pressure.

Because of the lack of localizing signs, a ventriculogram was made on March 23, 1927. The ventricular system was displaced to the left (fig. 1). On March 26, 1927, a large flap on the right side was reflected, and a typical subdural hematoma was exposed. This extended from the frontal region to the posterior parietal region, and when it was incised about 100 cc. of old blood escaped. As much of the membrane as possible was removed, and the wound was closed in the usual way.

The postoperative course was entirely uneventful. At the time of discharge, on April 29, the patient was in excellent condition, and the neurologic examination showed no abnormalities.

Comment.—In spite of the huge hematoma, there were no localizing signs. This was the first case in which a flap was reflected, and the results were excellent. The patient was the youngest in the series.

CASE 4.—D. W., a white girl aged 17 referred by Dr. Frank Harrison, of Dallas, and Dr. H. V. Copeland, of Grand Prairie, Texas, was admitted to the Barnes Hospital on May 4, 1928. There was no definite history of injury. Five months prior to admission the patient had an attack of unconsciousness, lasting for about five minutes, with no convulsive movements. She had four attacks similar to the first at intervals of about a month, without residual symptoms until the last attack, eight days prior to her admission, which was followed by extreme frontal headache, nausea and vomiting. Shortly before admission, she had noticed that her vision was becoming poor and that she did not see as well to the right side as to the left. A few days before admission, she had noticed double vision and an inability to control accurately the movements of her left arm and hand.

Neurologic examination showed bilateral choked disk, lateral nystagmus, marked ataxia of the left hand and questionable weakness of the abdominal reflex on the left. The visual fields were normal. It was felt that the most probable

Fig. 1 (case 3).—The displacement of the ventricular system to the left side as a result of the subdural hematoma on the right side.

diagnosis was a tumor of the posterior fossa, but since the symptoms were rather indefinite, injection of air was necessary.

On May 10 an incision was made over each occipital pole and both ventricles were found collapsed. Only a few cubic centimeters of fluid was obtained, and this was replaced with air. The plates showed no air in the ventricular system. Because of the smallness of the ventricles, it was very unlikely that there was a tumor of the posterior fossa; so because of the possibility of a frontal lesion on the right side a subtemporal decompression was made on the same side on May 16. When the bone was opened, the dura looked bluish, and when the dura was opened, some clot and old liquid blood escaped. The opening in the dura was made as large as possible and the wound closed.

Following operation, the choked disks did not subside. The patient's symptoms improved very little, and on May 23 a frontal flap on the right side was reflected, and a typical subdural hematoma, which in places seemed rather old, was exposed and removed.

The patient's postoperative course was uneventful. At the time of discharge, on the first of June, she was walking without difficulty. She has been perfectly well since.

Comment.—Several interesting facts are illustrated by this case. There was again no history of injury. It is not at all unusual for this condition to be confused clinically with a lesion of the posterior fossa. Even in skilled hands ventriculography is not always easy or absolutely diagnostic. The results are interesting in connection with the recent controversy as to the best method of treatment. Putnam and Cushing [3] expressed the opinion that "on the whole a generous exposure of the lesion by osteoplastic resection with or without combined subtemporal decompression to accommodate the subsequent edema would seem to be the preferential method." Fleming and Jones [10] recently reported a series of eight cases in which the patient was treated by making anterior and posterior perforator openings and washing out the blood and clots contained in the sac. There was only one death in the series. McKenzie [9] felt that a large flap is usually unnecessary and may be dangerous. He added two cases to his original series, making a total of eleven cases. Of this number, five patients were operated on by the method of osteoplastic flaps with one death, and six had a small opening in the bone for drainage only. All six patients recovered. He stated the opinion that only one opening is necessary and that the subdural space should be drained for forty-eight hours. Rand [14] stated that the type of operation should be determined by the condition of the patient and that while he usually reflected a flap any procedure which evacuates the contents of the sac will give good results. The case just reported may be similar to that reported by McKenzie [9] as an instance of reformation of a hematoma, probably from postoperative oozing.

CASE 5.—W. M., a Negress aged 24, was admitted to the Barnes Hospital on Feb. 6, 1930. Nine days before admission, during a period of intoxication, the patient was struck on the head with a lead pipe. She was unconscious for from ten to fifteen minutes. Since that time she had had headaches, and double vision had developed. At the time of admission she was somewhat stuporous, and her memory was very poor. There were numerous râles in her chest, and roentgen examination showed pulmonary tuberculosis.

Neurologic examination revealed little except complete paralysis of the third nerve on the right side. The eyegrounds were practically normal. The pulse rate was around 50 and the respiratory rate 12.

On February 10, because of increasing stupor, a subtemporal decompression was done on the right side. The dura was very tense and bluish, and when it was opened about 4 ounces (120 cc.) of old blood escaped. The cortex was markedly collapsed. A drain was put in, and the wound was closed.

14. Rand, C. W.: Chronic Subdural Hematoma, Arch. Surg. **14**:1136 (June) 1927.

The patient's postoperative course was complicated by a flare-up of the pulmonary tuberculosis and the development of an abscess in the lung. She was discharged on April 8 in fairly good condition.

She was readmitted to the medical service of the hospital on June 25 because of pulmonary tuberculosis. The sputum contained tubercle bacilli, and roentgen examination showed evidence of tuberculosis at that time, but the neurologic condition was good. The patient was discharged on August 7, not greatly improved.

Comment.—Decompression was performed in this case because the condition of the patient did not justify a more formidable procedure. The results were good. Here again there was a great scarcity of localizing signs, but paralysis of the oculomotor nerve has not been uncommon in this series. In this case evacuation of the contents of the sac through a small opening was all that was necessary.

Case 6.—M. G., a white woman aged 60, referred by Dr. Francis Camp, Springfield, Mo., was admitted to the Barnes Hospital on March 17, 1930. There was no history of preceding trauma. A week before admission the patient acquired a very severe headache accompanied by vomiting. She became unconscious and had several generalized convulsions, and at the time of her admission to the Barnes Hospital she had been unconscious for three days.

Neurologic examination showed a patient in profound coma. Her eyegrounds were normal. There was a scar of an old corneal ulcer on the left eye. There were no signs of meningeal involvement and no other neurologic abnormalities except bilateral Babinski and Oppenheim reflexes. The pulse rate was rather slow. Roentgenograms of her skull showed no abnormalities. It was felt that this probably was not a condition requiring surgical intervention and that such intervention would be unwise. She was transferred to the neuromedical service and gradually increasing hyperpyrexia developed. Unconsciousness persisted, and she died on March 22, 1930.

Autopsy was performed. Over the left cerebral hemisphere the dura was greenish blue, and a typical subdural hematoma was present. It extended over the entire cerebral hemisphere on the left side with the exception of the tip of the temporal lobe. No fracture could be made out. In addition, the patient had aspiration pneumonia.

Comment.—Here again there was no history of trauma, and as the eyegrounds were normal, an incorrect diagnosis was made. Ventriculography, or better still exploratory perforator openings, would have made a correct diagnosis possible. However, the condition of the patient was such that surgical intervention was not considered.

Case 7.—R. A., a white boy aged 10 years, was admitted to the Children's Hospital on Dec. 17, 1930. There was a definite history of injury a month before admission, when he fell off a hay stack and struck his head. There was no loss of consciousness. The next day he complained of headache, vomiting and double vision. However, his mother said that the child had complained of headache for several months before the fall and that she did not believe the fall had anything to do with the present condition. His headache and diplopia had increased, and his vision was becoming impaired.

Neurologic examination showed bilateral choked disks with hemorrhage, weakness of the left sixth nerve, facial weakness on the right side, weakness of the right hand, hypo-active deep reflexes, an Oppenheim sign on the right and nystagmus, more to the right than to the left. A roentgenogram showed a pressure skull. The preoperative diagnosis was cerebellar tumor, but because of the scarcity of definitely localizing signs, it was thought that it would be wise either to give an injection of air or to make a ventricular estimation.

On December 22 openings were made over the occipital poles for injection of air, and when the dura on the left side was opened, a typical subdural hematoma was exposed. A small amount of this was removed, and it was decided not to do anything further at that time.

The child's condition remained apparently the same after this procedure, and on December 30 his father took him out of the hospital under protest, in spite of the fact that the danger to the child's vision had been explained to him.

On Feb. 26, 1931, he was readmitted. At that time he still had bilateral choked disk and nystagmus. The abdominal reflex on the right was less active than that on the left.

On March 5, 1931, ventricular injection of air was made through the opening that had been previously made on the right side. The plates showed that the ventricular system was pushed over to the right side; so a flap was reflected on the left side. A typical subdural hematoma was exposed. When it was incised, a large amount of old blood escaped, and the membrane was then stripped from the cortex. The wound was closed with silk in the usual way.

The postoperative course was uneventful, with the exception of slight trouble with fluid under the flap. At the time of his discharge, on March 15, the patient was in very good condition.

Comment.—This is another example of the excellent results obtained in a child, and again the question of small openings versus a large flap is raised. From the operative note it seems that there was certainly not complete evacuation of the contents of the sac through the small opening, and this may easily explain the lack of improvement.

Case 8.—M. R. V., a white man aged 45, referred by Dr. George B. Fletcher, Hot Springs, Ark., was admitted to the Barnes Hospital on April 5, 1932. This patient had been a moderate drinker of alcoholic liquors up to the year before admission, but during the past year he had been a sporadic dipsomaniac. For about ten months the patient's wife felt that he had been more irritable than usual, and on several occasions he had threatened suicide. Nine days before admission he went on one of his periodic sprees, and that evening he was found unconscious on the floor of his hotel room. During the next few days he was stuporous most of the time and complained of severe headache.

At the time of admission, he was stuporous but could be aroused. His memory was very poor, and he was disoriented. There was some tenderness in the left parietal region. His eyegrounds were normal. There was a questionable weakness on the right side of the face, and bilateral pathologic toe signs. The spinal fluid was yellow, and the pressure was 160 mm. of water. There were 90 cells without acetic acid and 45 cells with acetic acid. Roentgen studies showed a linear fracture in the parietal region with no depression. Wassermann tests on the blood and spinal fluid gave negative results.

Because of the definite history of alcoholism, the diagnosis was rather obscure. However, it was felt that the most probable diagnosis was chronic alcoholism complicated by the fracture of the skull.

About thirty-six hours after admission the patient became comatose, the blood pressure suddenly rose to 210 and the respirations became very labored. Death ensued in a short time.

At autopsy several fractures were noted in the left temporoparietal region, with a large subdural hematoma over the entire right hemisphere. The other organs showed no changes.

Comment.—In this case operation was never considered. The diagnosis was missed entirely in spite of the definite history of trauma, slightly increased spinal fluid pressure and yellow spinal fluid. Again there is established the fact that a chronic subdural hematoma frequently shows no localizing signs. Had exploratory perforator openings been made or ventriculography been performed soon after admission, the outcome might have been different. This case also serves to emphasize the point that the only treatment of any avail is surgical removal of the clot. Lumbar puncture not only brings about no improvement but may be dangerous.

Case 9.—H. R., a white man aged 65, referred by Dr. O. D. Stanley, of Decatur, Ill., was admitted to the Barnes Hospital on July 6, 1932. Three weeks before admission he was in an automobile accident. He was unconscious for several hours but was apparently normal and was attending to his usual duties at the end of five days. Five days prior to admission he became unconscious and was taken to a hospital in another city, where hemorrhages in the eyegrounds were discovered. After he recovered consciousness somewhat, he was unable to move his left arm. His pulse had been rather slow. There had been no vomiting. At the time of admission he was markedly stuporous. The left eyeground showed a typical choked disk with large hemorrhages, while in the right eye the margins of the disk were blurred and the veins full but there were no hemorrhages. There was a flaccid type of paralysis of the left arm and pathologic toe signs in the left leg. The diagnosis was subdural hematoma on the right side.

The patient was markedly dehydrated, and his stupor progressed to coma. After fluid had been given intravenously and subcutaneously, a flap was reflected on the right side on July 7. A perforator opening was made first to see if the clot could be washed out, but this was impossible, so a flap was reflected. The subdural hematoma was removed and the wound closed in the usual way.

Shortly after operation, the patient would respond but would immediately lapse into a rather deep stupor. This condition gradually improved, and he seemed to be in fairly good condition until the fourth postoperative day, when he began to have convulsions on the left side. These convulsions continued throughout the next day, and at that time he showed definite evidence of bronchial pneumonia. He was put in an oxygen tent, but in spite of all treatment he grew steadily worse and died on the eighth postoperative day.

At autopsy there was a fracture of the posterior wall of the frontal sinus on the left side with an area of infection at the site of the fracture. From this area a sinus extended back along the left side of the falx and a short distance back it eroded through the falx and extended into a large abscess in the right frontal lobe. In addition, there was evidence of severe bronchial pneumonia.

Comment.—This case illustrates forcibly that an apparently mild injury to the head may have serious complications. Since in the cases that have been cited prior to this one there were few localizing signs, it may be assumed that this patient's symptoms were due more to the abscess than to the hematoma. In reviewing the case, one might assume that his failure to improve should have suggested ventriculography or reexploration. However, a man of 65 who was at the point of death on admission was not a good subject for surgical treatment; consequently to do as little as possible was considered the wise policy.

In this case also an attempt to utilize a small opening in the bone was unsuccessful.

CASE 10.—S. M., a white man aged 65, referred by Dr. Charles Compton, of Springfield, Ill., was admitted to the Barnes Hospital on Nov. 1, 1932. Two months before admission the patient, who was sheriff of his county, was struck during a fight. He fell and hit his head on the concrete walk and sustained a fractured skull. He remained in a hospital in another city in a semiconscious state for about a week. At the end of the week, lumbar punctures and hypertonic solutions resulted in some temporary improvement, but he soon became irrational and very difficult to manage. Two weeks before admission to Barnes Hospital, he left the local hospital and was taken home. While at home he had rather marked mental symptoms with delusions of persecution, and he refused to eat. There had been a few times when the patient seemed fairly alert mentally, but the family became alarmed because of marked loss of weight and he was brought to Barnes Hospital. A diagnosis of posttraumatic psychosis was made, and he was transferred to the service of Dr. A. D. Carr.

On November 4, the patient had a focal convulsion involving the right side of the face and the right arm and leg. However, it was not believed that his condition required surgical treatment. He remained in the hospital with periods of complete irrationality alternating with periods when he was fairly alert mentally until the latter part of January. At that time he was definitely going downhill, so it was decided to perform an exploratory operation.

A perforator opening was made over the right frontal lobe, and a subdural hematoma was immediately seen. A moderate-sized flap was reflected, and it was then seen that the hematoma was very small, covering only the surface of the frontal lobe. There were numerous adhesions between the cortex and the dura, and the cortex was yellowish in several places. The small subdural hematoma was completely removed.

Following operation, the patient improved rather remarkably and was discharged on March 7. At that time he was still having periods of slight mental confusion, but for the most part he was well oriented and seemed to be in excellent condition.

Comment.—This case is an excellent example of a fact emphasized by Fleming and Jones,[12] i. e., that this condition may easily be mistaken for a posttraumatic psychosis. The convulsion occurred on the same side as the hematoma. It is still difficult to believe that this small lesion was responsible for all of the symptoms, but the fact remains that there was marked improvement after operation.

In this case the diagnosis of subdural hematoma was made by the use of a small opening in the bone, but no attempt was made to evacuate the contents of the sac through this opening.

Case 11.—J. G. M., a white youth aged 21, referred by Dr. A. B. Jones, of St. Louis, was admitted to the Barnes Hospital on Feb. 1, 1933.

There was a definite history of injury three months before admission. The patient was in an automobile accident and received a severe blow on the head, which resulted in unconsciousness and lacerations of the scalp. The lacerations of the scalp were sutured, and as the patient recovered consciousness shortly after, he was allowed to go home from the local hospital. Afterward he had infrequent headaches for two months. A month prior to admission the headaches became almost constant, and he noticed blurring of vision.

Fig. 2 (case 11).—Normal ventricular configuration in spite of a large subdural hematoma on the right side.

At the time of admission neurologic examination showed bilateral choked disks, facial weakness on the left side, central in type, an Oppenheim sign on the left and slight diminution in the abdominal reflex on the left. A calcified pineal gland was shown on roentgen examination, and this was displaced to the left of the midline. The preoperative diagnosis was a lesion in the right frontal lobe, either subdural hematoma or tumor.

On February 6 a ventriculogram was made. About 8 cc. of air was put into the left ventricle. Since this air would not go across into the right ventricle, air was put into the right ventricle. The plates looked normal (fig. 2). In spite of the normal ventriculogram, however, a cerebral flap was reflected on the right side and a very large subdural hematoma was exposed and removed. A subtemporal decompression was left.

At the time of his discharge, the condition of the patient was excellent with the exception of choked disks, which were still present but were subsiding. He has been seen at intervals since his discharge and is normal in every respect.

Comment.—This case is interesting in retrospect. In spite of the definite history of trauma, the possibility of tumor was considered strongly enough so that ventriculography was considered wise. The ventricular system was apparently normal in configuration, but it was impossible by rotation of the head to get the air to pass from the left into the right ventricle. Had the openings for ventriculography been made over the region of the anterior horns instead of over the posterior horns, ventriculography would not have been necessary.

This is also the first case of subdual hematoma in which it was possible to utilize the pineal shift described by Naffziger,[15] and it is difficult to understand how, although the pineal body was displaced, the ventricular system was in the normal position.

This is the first case in this series in which accurate localizing diagnosis by neurologic examination was possible. The smooth convalescence with prompt and complete recovery shows the great advantage in being able to treat a patient fairly early in the course of the disease.

CASE 12.—H. B. G., a dentist, aged 54, was admitted to the Barnes Hospital on Feb. 22, 1933.

There was a definite history of injury six weeks before, when the patient slipped on the ice and struck his head. He was unconscious for a very short time. The next day he returned to his usual work and had no further symptoms except that he complained of headache and general weakness. About two weeks after the injury the headaches became much more severe and were accompanied at times by nausea and vomiting. He acquired rather marked mental symptoms, which had progressed. He slept a good part of the time and was much confused. Two days before admission to the hospital, he was seen by Dr. Ernest Sachs at home. At that time he was absolutely unmanageable and examination was out of the question. He was admitted to the hospital as a patient of Dr. A. D. Carr, and a careful lumbar puncture was made, which showed the pressure of the spinal fluid to be 400 mm. and the cell count 3. He was given paraldehyde to quiet him and soon dropped into a deep stupor, from which he could not be aroused. He was transferred to the neurosurgical service in deep coma. His eyegrounds were practically normal. The preoperative diagnosis was either subdural hematoma or a tumor of the frontal lobe, and on February 24 a ventriculogram was made (fig. 3). The roentgenograms showed a frontoparietal lesion on the left side; so a flap was reflected on the left side. A rather large subdural hematoma was exposed, and about 150 cc. of unclotted blood was removed, together with as much of the membrane as possible. When the wound was perfectly dry it was closed in the usual way.

The immediate postoperative condition was rather precarious, but after transfusion the blood pressure rose. However, on the following day the temperature was elevated and he was slightly cyanotic. Hyperpyrexia became marked, the patient's condition rapidly grew worse, and he died about forty-eight hours after operation.

Autopsy was performed and showed that the subdural hematoma had been completely removed. The cortex was still rather markedly compressed and there

15. Naffziger, Howard: A Method for Localization of Brain Tumors: The Pineal Shift, Surg., Gynec. & Obst. **40**:481, 1925.

was some extradural clot, but not enough to account for the symptoms. The patient also had well developed bronchial pneumonia.

Comment.—This case illustrates the fact that psychotic symptoms are frequent and may be severe. The history was rather confusing, for some of the patient's associates stated that he had acted rather peculiarly before the accident, and there was also a suspicion that he had become addicted to some drug.

Much thought has been given to the part that the paraldehyde played. It was given in the usual dose, but after sleep was induced the patient could not be aroused, and his coma was so deep that no anesthesia was needed for the operation.

Fig. 3 (case 12).—Displacement of the entire ventricular system to the right side by the subdural hematoma on the left side.

The lumbar puncture has also been considered, but since it was done very cautiously, with the removal of only a few drops of fluid, it probably had nothing to do with the outcome.

Case 13.—A. H., a white woman aged 47, referred by Dr. Charles Duden, of St. Louis, was admitted to the Barnes Hospital on June 10, 1933. She came in almost immediately following a fall down a flight of six steps. Immediately after the injury, she was not unconscious but soon became somewhat stuporous, and at the time of admission, although easily aroused, she would drop off to sleep if left alone. The only neurologic signs were a Babinski sign on the right and an Oppenheim sign on the left. A roentgenogram showed a fracture in the right parieto-occipital region, with no depression.

She was treated with hypertonic solutions and seemed to do extremely well until the sixth day, when she had several brief convulsive attacks characterized by drawing of her head and eyes to the left. She also had one generalized convulsion. The next day she had several brief convulsions, and beginning choked disks were noted. A diagnosis of subdural hematoma was made. Since there were no localizing signs, it was decided to make perforator openings over both frontal lobes and in this way to determine the site of the hematoma.

The perforator opening on the right side was made first, since this was the side of the fracture, and the subdural hematoma could be seen. A small flap was reflected, and when the dura was opened about 90 cc. of old blood escaped. The typical membrane of a subdural hematoma was removed and the wound closed in the usual way.

The patient's postoperative course was entirely uneventful, and she was discharged at the end of the second postoperative week.

Comment.—This is one of the rare cases in which the condition develops under one's eyes, so to speak. The symptoms began so soon after injury that one is not sure whether it is properly called *chronic* subdural hematoma, but the subdural membranes were well formed. The excellent results show the advantage of early recognition.

Case 14.—W. V. M., a white man aged 49, referred by Dr. R. M. Purdie, of Houston, Texas, was admitted to the Barnes Hospital on July 16, 1933. He was a farmer and gave no definite history of injury. His illness began about eighteen months before, with headache and vomiting. This condition had become progressively worse, and for the past two to three months there had been an increasing diminution in the acuity of vision. About a month before admission there was an unusually severe attack of headache and vomiting, with questionable loss of consciousness. After this his memory became markedly impaired, and an athetoid tremor of both upper extremities developed.

Neurologic examination showed a marked decrease in visual acuity with slight papilledema in both eyes, diminished hearing in both ears, athetoid movements of the upper extremities and hyperactive deep reflexes with pathologic toe signs on the left, but because of the scarcity of localizing signs ventriculography was necessary. The diagnosis was probable tumor of the frontal lobe.

The ventriculogram, made on July 19, showed a displacement of the ventricular system to the left. A flap was reflected on the right side. A subdural hematoma, about 1.5 cm. in thickness, was exposed and removed. There was marked atrophy of the convolutions beneath the subdural hematoma. A small piece of this atrophied cortex was removed for section.

The patient talked very well and seemed entirely rational about six hours after the operation, but at the end of fifteen hours he began to be very drowsy and difficult to arouse. This was attributed to cerebral edema, and he was treated with hypertonic solutions, with slight temporary improvement. The following day he took fluids and tried to talk. His temperature was rather markedly elevated, and on July 22, because of the possibility of a postoperative clot, a portion of the wound was reopened, but no clot was found. The following day, the patient had well developed bronchial pneumonia; his condition grew steadily worse, and he died on the fourth postoperative day.

Autopsy was performed, but no evidence of postoperative bleeding was noted in the cranial cavity. There was well developed bronchial pneumonia.

Comment.—This case again illustrates: (*a*) the ease with which the causative trauma may be overlooked, and (*b*) the scarcity of localizing signs. In retrospect, one wonders if a less formidable operation might have influenced the result.

Case 15.—R. A., a white boy aged 15, referred by Dr. H. A. Kuhn and Dr. Ray Elledge, of Hammond, Ind., was admitted to the Barnes Hospital on Feb. 20, 1934. Three years before admission he was hit by a baseball bat in the temporal region on the left side. He had apparently been perfectly well until five months before admission, when he began to complain of occasional headache. These headaches persisted until a month before admission, when diplopia developed, followed shortly by complete paralysis of the third nerve on the left side. About a month before admission he began to have nausea and vomiting, and this had persisted at intervals until the time of his admission to the hospital. Two weeks before admission he had an attack of unconsciousness, without a convulsion, which lasted for several hours.

Neurologic examination showed paralysis of the third nerve and facial weakness on the right side, an Oppenheim sign on each side and a tendency to stagger to the right when walking. His eyegrounds were normal.

On February 24 a ventricular injection of air was given. The roentgenograms showed the ventricular system pushed over to the right; so a flap was reflected on the left side. The dura had the typical greenish-blue appearance of a subdural hematoma. The subdural hematoma covered part of the temporal lobe, a portion of the occipital lobe and all of the parietal lobe. A large amount of old bloody fluid, of chocolate color, escaped during operation. All of the membrane was removed and the wound closed in the usual way.

Following operation, the patient was totally aphasic, and the next morning he had a convulsion, which started in the right side of his face and became general. Following the convulsion he became extremely restless; so the flap was reopened. A fairly large clot between the bone and the dura was removed, but there was no evidence of subdural bleeding.

His general condition improved. He was totally aphasic for three days, when his speech gradually began to return. He was discharged on March 8. At that time the paralysis of the third nerve on the left side was still practically complete, and pathologic toe signs were still present, but the facial paralysis and aphasia had entirely cleared up.

Comment.—If the history was correct, this patient had a latent interval of three years. In the series of sixteen cases the shortest latent interval was six days and the longest three years. If the increase in size of a hematoma is due to repeated hemorrhages, as has been stated by Trotter,[2] Putnam and Cushing,[3] Keegan [6] and others, there must have been some unusual factor in this case which brought about a renewed hemorrhage after a long interval of latency. On the other hand, one finds it extremely difficult to believe that it would take almost three years for the protein molecules of the blood in the sac to break down and osmosis to begin, as suggested by Gardner [10] and Zollinger and Gross.[11]

It is also difficult to explain paralysis of the third nerve on the right side with a subdural hematoma on the left. In this series, involvement

of the third nerve was noted in three cases. In two of these cases it was contralateral and in one homolateral.

CASE 16.—L. B., a white man aged 28, referred by Dr. Charles O. Lane, of West Frankfort, Ill., was admitted to the neuromedical service of the Barnes Hospital on July 27, 1934.

Exactly three months before admission the patient had received a blow on the head which made him unconscious for a few minutes. There was apparently a complete recovery from this, and the patient soon resumed his normal activities. Two and one-half weeks before admission he noticed that his vision was rapidly failing and he had a very severe headache. He also had nausea and vomiting, and the headache, nausea and vomiting continued up until the time of admission. The headache had been so severe that he had been confined to his bed continuously, and his vision had rapidly diminished.

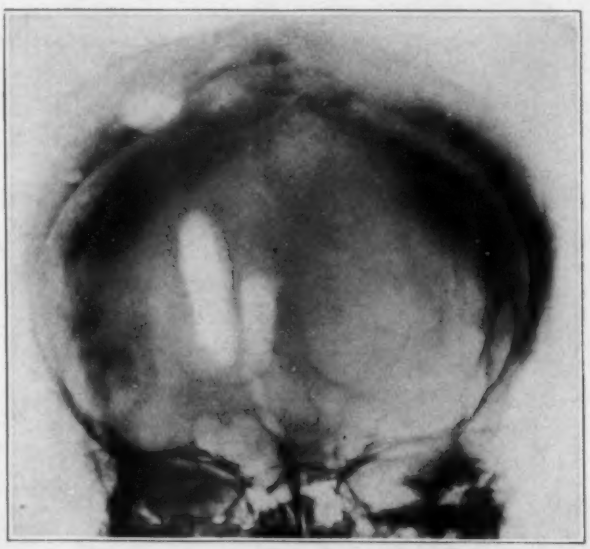

Fig. 4 (case 16).—Dislocation of the ventricular system to the left side and compression of the right ventricle as a result of the subdural hematoma on the right side.

Neurologic examination showed marked diminution in the acuity of vision, bilateral choked disk with many hemorrhages and much exudate, lateral nystagmus, most pronounced on looking to the left, slight incoordination of the left hand and hypo-active deep reflexes. Roentgenograms showed marked pressure skull with the dorsum slightly forward.

With the definite history of injury, subdural hematoma was considered to be the most likely diagnosis, but because of the signs indicating involvement of the cerebellum ventriculography was necessary. This was performed on July 30. The entire ventricular system was found pushed over to the left (fig. 4); so a large flap was reflected on the right side. An enormous subdural hematoma was exposed and removed. When the most medial portion of the sac was removed, the dura over the longitudinal sinus was stripped from the bone; there was considerable troublesome bleeding, but this was finally controlled with a piece of muscle.

The patient's postoperative course was considerably prolonged because of repeated accumulations of fluid under the flap. He was discharged on August 21. At that time he was normal in every way except that the choked disks had not completely subsided.

In October 1934, the patient had a very severe seborrheic dermatitis around the incision. There was marked cutaneous irritation with some drainage for about two months. Roentgen examination at that time showed a possible slight area of osteomyelitis along the edge of the bone flap. On December 1 a portion of the incision was opened and a small bit of bone was removed. One or two silk sutures were also removed from the wound, and it was allowed to granulate in slowly. He was discharged from the hospital on December 29, and in a letter a month later he said that his scalp had entirely healed and that his condition was excellent.

Comment.—In spite of a definite history of injury three months before, the presence of neurologic signs that are usually seen with a cerebellar lesion made it necessary to give an injection of air. The convalescence in this case was greatly prolonged as a result of accumulations of fluid under the flap, and the prevention of this has been one of the arguments advanced in favor of the small opening in the bone.

ANALYSIS OF SYMPTOMS

Since in cases of chronic subdural hematoma the symptomatology is extremely variable and frequently misleading, an analysis of the prominent symptoms in this series of cases is of value (table 1).

TABLE 1.—*Analysis of Symptoms*

	Forty-Two Cases (Jelsma)	Eleven Cases (McKenzie)	Seven Cases (Rand)	Sixteen Cases (Sachs and Furlow)
History of trauma	88%	91%	100%	80%
Male	93%	82%	100%	68.75%
Female	7%	18%	0%	31.35%
Headache	79%	100%	86%	88%
Choked disks	40%	91%	72%	68.75%
Reflex changes	56%	36%	56%	62.5%
Mental changes	86%	18%	56%	50%
Drowsiness	79%	90%	50%	50%
Cranial nerve changes	47%	9%	50%	50%
Vomiting	29%	54%	42%	44%
Motor disturbances	70%	55%	28%	36%
Coma	57%	28%	56%	30%
Nystagmus	11%	0%	14%	18%

Jelsma [16] analyzed the symptoms in forty-two cases reported in the literature and two cases of his own. McKenzie [9] tabulated the symptoms in nine of his cases for comparison with those of Jelsma,[16] and for completeness the two cases subsequently added by him were included in the tabulation, as was an analysis of the seven cases reported by Rand.[14] Ages of patients are not included, for the lesion may be present

16. Jelsma, Franklin: Chronic Subdural Hematoma, Arch. Surg. **21**:128 (July) 1930.

at any age. In this series the youngest patient was 4 years of age and the oldest 65. Rand [14] reported one case in a man 90 years old.

As shown in table 1, the history of trauma is frequently obtained, and since trauma is the etiologic factor it is easy to understand why the lesion is so much more frequent in men than in women.

Headache is the most common complaint and choked disks the most common finding. Since the great majority of the cases analyzed by Jelsma [16] were reported by others, this might account for the low incidence of choked disks in his series. Pathologic reflexes are also common, but these reflex changes are frequently of no localizing value. In this series, ten patients had reflexes that were abnormal, and in five instances the pathologic reflexes were contralateral, in four cases bilateral, and in one homolateral.

Jelsma [16] emphasized the frequency of mental changes; while they were common, the incidence in this series was much lower than in his.

The frequency of occurrence of other signs may be seen in the table. An analysis will show merely that localization is frequently impossible by neurologic signs alone.

RESULTS AND CONCLUSIONS

Since this is one of the largest reported series of cases of chronic subdural hematoma from a single clinic, data on the final results are of value (table 2).

TABLE 2.—*Analysis of Final Results in Sixteen Cases of Chronic Subdural Hematoma (Sachs and Furlow)*

Number of Cases	Number	Recoveries	Deaths	Mortality Rate, Percentage
Total	16	10	6	37.5
Operated on	14	10	4	28.5
In comatose state	5	0	5	100
Conscious	11	10	1	9

There was a total of sixteen patients, and of these, six died, making a total mortality rate of 37.5 per cent. However, in two instances the condition was not correctly diagnosed, and operation was not performed. In each case the result was fatal. The operative mortality is based on four fatalities in fourteen cases, or 28.5 per cent. Further analysis shows that five patients were admitted in coma or became comatose soon after admission, and all died, giving a mortality rate of 100 per cent for comatose patients. There were eleven patients who were conscious. Of these patients, only one died, giving a mortality rate of only 9 per cent in this group.

This striking fact is worthy of emphasis: When the diagnosis was made and operation performed before the onset of coma, there was a mortality rate of only 9 per cent, but if operation was delayed until after the onset of coma and symptoms of marked compression, the mortality rate was 100 per cent.

For purposes of comparison, mortality rates in other reported series of cases of chronic subdural hematoma are shown in table 3.

As a result of the facts brought out in this series of cases, it is felt that the following opinions and conclusions are justified:

Chronic subdural hematoma frequently produces very few localizing signs. The three most important points in diagnosis are: (1) the history of injury; (2) headache, and (3) choked disks. However, the condition may exist in the absence of any or all of these signs.

TABLE 3.—*Mortality Rates in Cases of Chronic Subdural Hematoma*

Authors	Total Number of Cases	Mortality, Percentage	Mortality After Operation, Percentage
Trotter [8]	4	50	50
Putnam and Cushing [2]	12	33⅓	33⅓
Rand [6]	7	28	16⅔
McKenzie [5]	11	9	9
Fleming and Jones [4]	8	12	12
Jelsma [13] (42 cases from literature and 2 cases of his own)	44	43.2	19.3
Sachs and Furlow	16	37.5	28.5

Ventriculography or exploratory perforator openings are very often necessary to make the diagnosis.

The surgical treatment of chronic subdural hematoma offers a good prognosis. However, the prognosis is vastly better if the patient comes to the hospital before the development of symptoms of marked cerebral compression.

The question of the best method of surgical approach is not definitely settled. It is my opinion that if the general condition of the patient is good the reflection of an osteoplastic flap is the method of choice. If the patient is in coma, I propose to modify the treatment, using the method of washing out the contents of the sac through two openings, as suggested by Fleming and Jones.[10] I do not believe that one opening, as suggested by McKenzie,[9] is always sufficient, and in support of my belief I cite three cases (cases 4, 7 and 9) in which this method failed.

AUTOTRANSPLANTATION OF PARATHYROID GLAND IN THE DOG

AN EVALUATION OF HALSTED'S LAW OF DEFICIENCY

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The factors which determine the survival of glandular transplants have interested investigators and clinicians for years. It has been generally found that the transplantation of tissue into an individual of the same species—homografting—or into an individual of a different species—heterografting—is unsuccessful, whereas the reimplantation of tissue into the same individual is frequently successful. Transplantation of the latter type, or autografting, is, however, not always successful. To explain the failures, it has been proposed that one of the important factors in determining the survival of autotransplants is the physiologic need of the organism for the tissue in question. Cristiani [1] was the first to suggest such a deficiency as a determining factor, for he found that thyroid tissue engrafted into rats survived only after a partial thyroidectomy had been performed. His conclusion does not seem justified, however, since the tissue which was successfully transplanted was an autograft, whereas that which was unsuccessfully transplanted, without partial thyroidectomy, was of necessity taken from another animal, and was therefore a homograft. Halsted [2] several years later arrived at a similar conclusion as a result of his experimental observations on autotransplantation of the parathyroid gland in dogs. He studied the effect of varying the degree of parathyroid deficiency on the viability of the transplant and concluded that the graft would not live unless a need for this graft had been created by excising more than one half of the previously existing parathyroid tissue. He found also that when two parathyroid glands were simultaneously transplanted under suitable conditions of deficiency, only one would survive. He therefore concluded that transplanted parathyroid tissue in excess of what is urgently required by the organism does not live. This concept has enjoyed wide recognition and indeed has frequently been referred to as "Halsted's law of deficiency." The teleologic implications of this

From the Laboratory of Surgical Research, Harvard Medical School.

1. Cristiani, H.: Evolution des greffes thyroïdiennes superflues, Compt. rend. Soc. de biol. **58**:361, 1905.

2. Halsted, W. S.: Auto- and Isotransplantation, in Dogs, of the Parathyroid Glandules, J. Exper. Med. **11**:175, 1909.

finding are of great importance in the general field of physiology as well as in the immediate experimental and clinical problems of glandular transplantation. In spite of this fact, a search of the literature fails to reveal further experimental study to corroborate or refute Halsted's conclusions.

As a preliminary to an experimental study to test this "law of deficiency," the protocols of Halsted's experiments, which are recorded in admirable detail, were carefully studied. It became apparent that the evidence, though suggestive, was not conclusive. The results of the experiments by no means uniformly supported the concept, nor were the experiments themselves drawn up in such a way as to put the hypothesis to a test. It was observed that in most of the experiments it was impossible to determine the extent of the parathyroid deficiency. In many of the experiments the degree of deficiency which had existed at the time the graft was placed was altered by the removal of additional parathyroid tissue a week or two later. In other experiments grafts were placed in dogs in which grafts had already been placed from one to two weeks previously, so that the degree of deficiency existing at the time the second graft was transplanted was indefinite, as it depended on the functional condition of the first graft. Moreover, in only three of Halsted's experiments were the results confirmed by microscopic study.

The following experiments were undertaken to determine the importance of the factor of deficiency on the immediate survival of glandular transplants. The parathyroid gland of the dog is well suited for such a study since there are four glandules with fairly constant anatomic distribution, i. e., two glandules associated with each lobe of the thyroid gland. The removal of all four glandules results in fatal tetany, while the removal of three is followed as a rule by mild transient tetany. One or two glandules can be excised without any physiologic embarrassment.[3]

METHOD

Autoplastic transplantation of the parathyroid gland was performed in a total of thirty-four dogs. Pentobarbital sodium (32 mg. per kilogram of body weight) administered intraperitoneally was employed as the anesthetic, and careful aseptic technic was observed. Each graft consisted of a single intact parathyroid gland which was reimplanted within a few minutes of its removal between the fibers of the adjacent muscles in the neck, with a silk suture placed to mark the location. The state of parathyroid deficiency was varied so that in one series only the one gland which was transplanted was molested, while the other three were not disturbed. In another series two glands were removed; one of these was grafted and the other discarded, while the two remaining glands were left in situ. In a third series all four of the parathyroid glands were removed, one

3. Morel, L.: Les parathyroïdes, Paris, A. Hermann & fils, 1912.

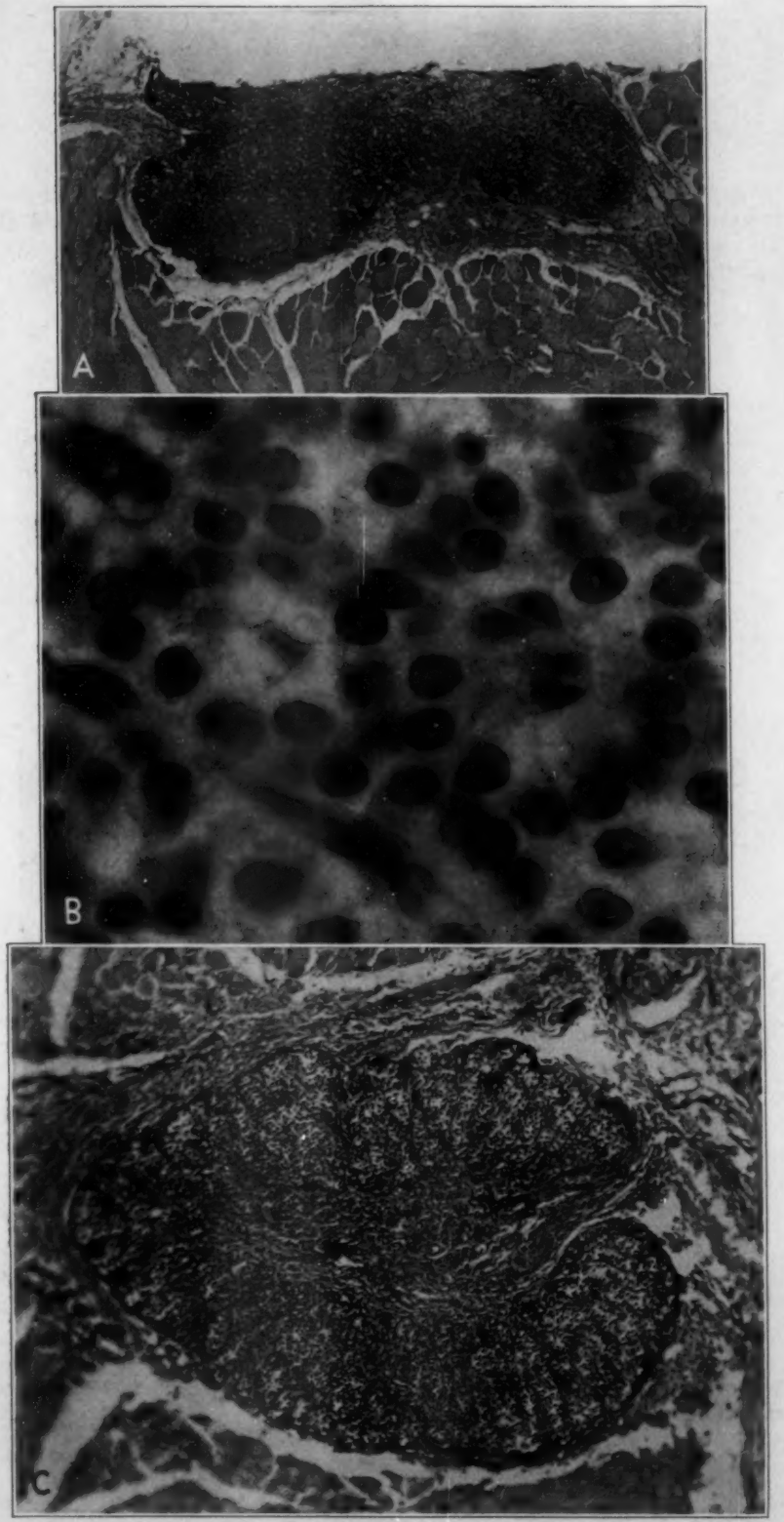

Fig. 1.—Sections of muscles containing grafts from dogs with a parathyroid deficiency of 25 per cent. *A* shows the section from dog C-11, from which one parathyroid gland had been removed and reimplanted into the muscle of the neck. The graft was excised after twenty-one days. *B* shows the same section under high power magnification. *C* is the section from dog C-136. The graft was excised after twenty-eight days. Removal of the remaining three parathyroid glands three days previously failed to cause tetany, indicating that the graft was functioning.

being replaced as a graft. Thus the state of deficiency varied from 25 to 100 per cent at the time the graft was placed. When only one parathyroid gland was removed great care was taken to disturb the thyroid gland as little as possible so as not to interfere with the blood supply to the second parathyroid

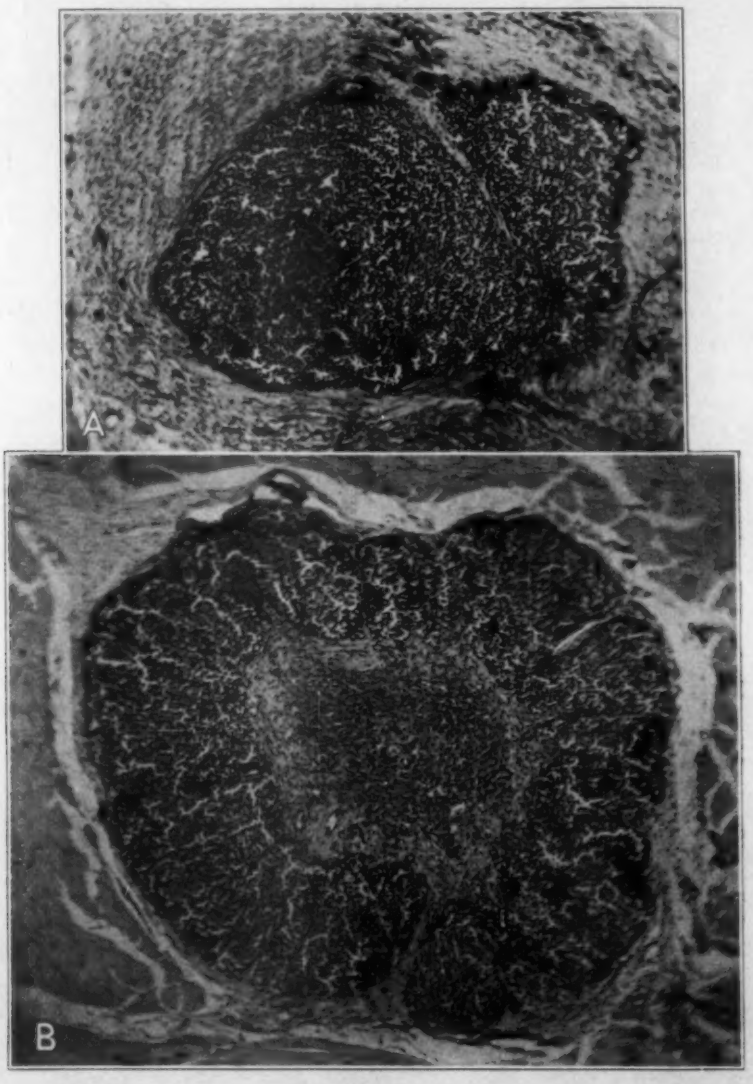

Fig. 2.—Sections of muscle containing grafts from dogs with a parathyroid deficiency of 50 per cent. The graft in *A* (dog C-164) was removed after forty-five days; that in *B* (dog C-343) was removed after sixty-nine days.

gland on the same side. When two parathyroid glands were removed, this was accomplished by performing a thyroparathyroidectomy on one side, and when all four parathyroid glands were removed bilateral thyroparathyroidectomy was

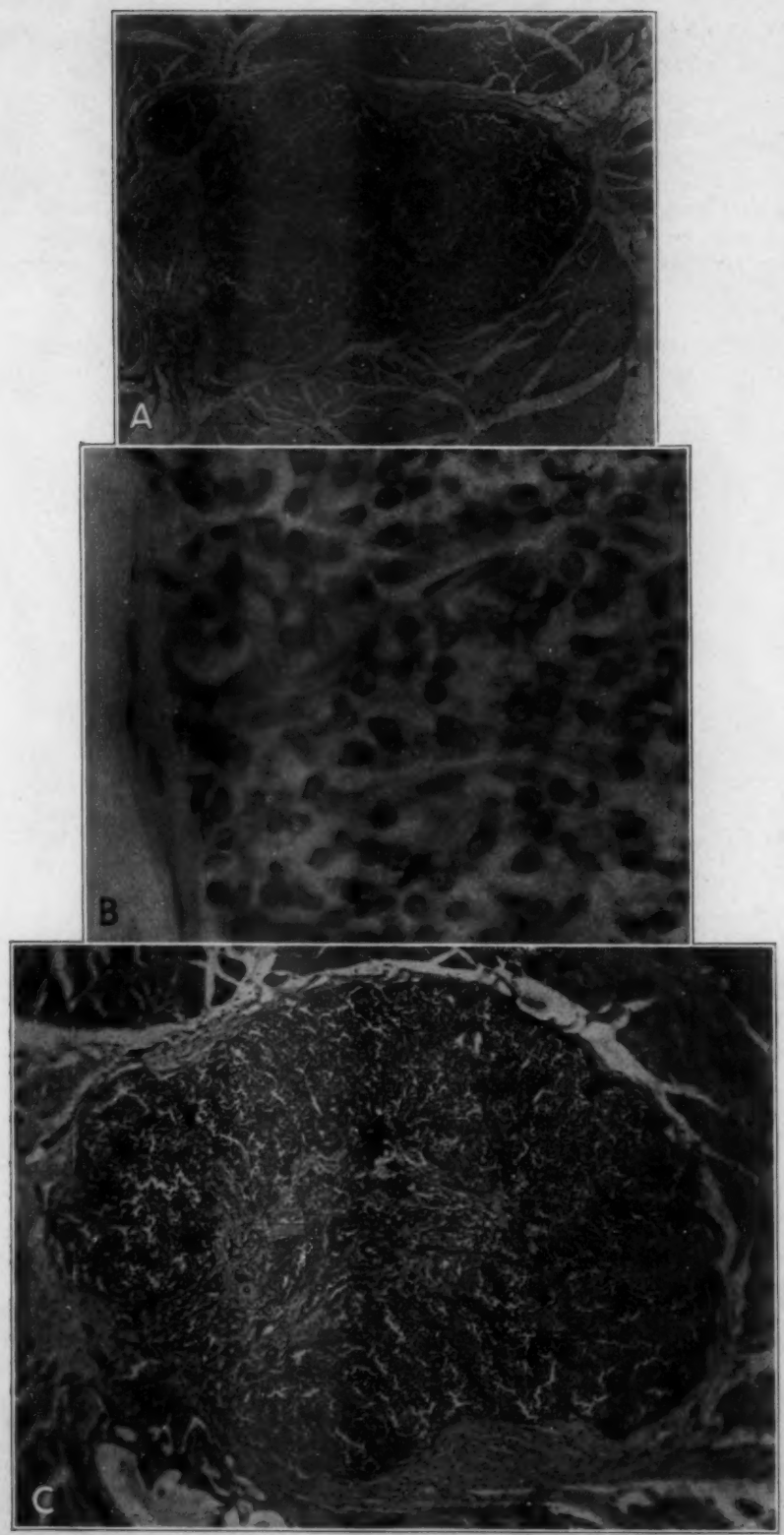

Fig. 3.—Sections of muscle containing grafts from dog C-60, with a parathyroid deficiency of 50 per cent. Two grafts were placed simultaneously, one in each side of the neck. *A* shows a graft removed from the right side after sixty days. *B* shows the same section under high power magnification. *C* shows the graft removed from the left side after sixty days.

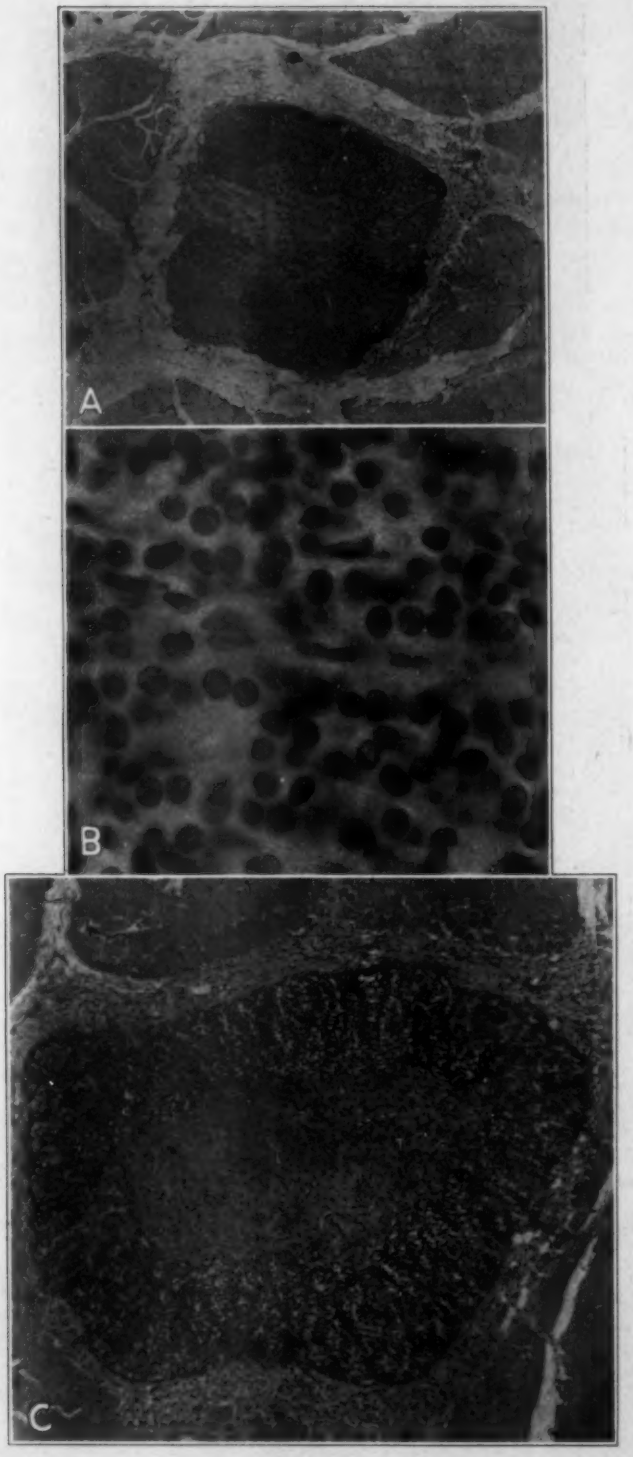

Figure 4, *A*, *B* and *C*.

Fig. 4.—Sections of muscle containing grafts from dogs with a parathyroid deficiency of 100 per cent. The graft in *A* (dog C-382) was removed after fourteen days. *B* is the same section under high power magnification. The graft in *C* (dog C-9) was removed after twelve days; that in *D* (dog C-18), after twenty-three days (fatal tetany developing after removal and indicating that the graft had been physiologically active), and that in *E* (dog C-10), after twenty-nine days, showing follicular changes occasionally seen in transplants of parathyroid tissue.

performed. Since a dog deprived of all four parathyroid glands will die of tetany within a few days unless proper measures are taken, the dogs in the latter group were prepared by giving them from 10 to 20 drops of viosterol daily for from two to three weeks before operation and calcium lactate by mouth for from one to two weeks postoperatively.[4]

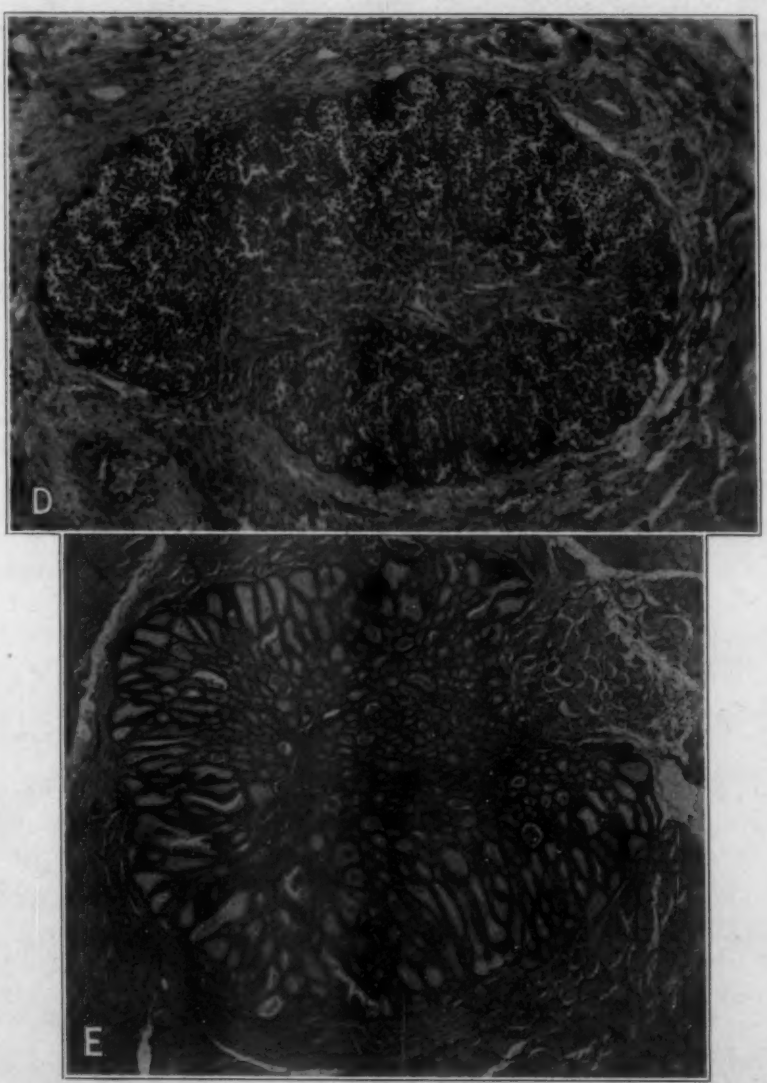

Figure 4, *D* and *E*

In several dogs two grafts were placed at the same time, one in the muscle on either side of the neck, to see whether, as Halsted had found, only one of these would survive. An attempt was made to prevent the survival of the graft in

4. Jones, J. H.; Rapoport, M., and Hodes, H. L.: The Effect of Irradiated Ergosterol on Thyroparathyroidectomized Dogs, J. Biochem. **86**:267, 1930.

several dogs by administering large doses of viosterol or parathyroid extract postoperatively—a possibility which comes to mind if the "law of deficiency" holds true. In three dogs in which a transplantation had been performed with a deficiency of only 25 per cent the functional as well as the microscopic survival of the graft was tested by removing the remaining three parathyroid glands at a second operation and observing the dog for tetany.

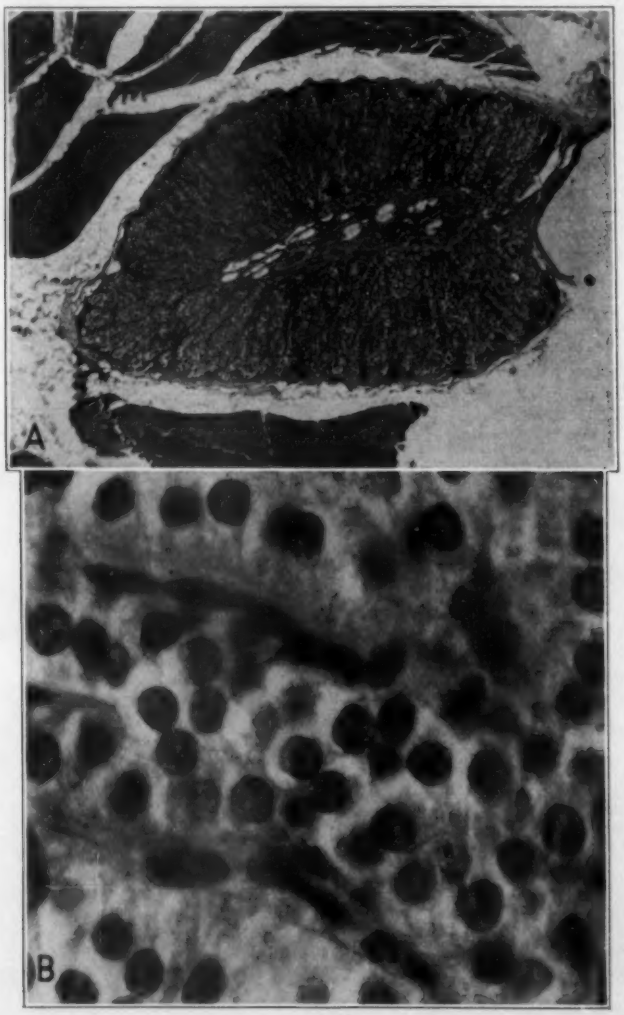

Fig. 5.—Section of muscle containing a graft from dog C-62, with parathyroid deficiency of 100 per cent. *A* shows the graft removed after sixty days. The dog had received 30 drops of viosterol daily since the time of grafting. *B* shows the same section under high power magnification.

After an interval varying from five to one hundred and thirty-four days the segment of muscle containing the graft was removed and examined microscopically.

RESULTS

Parathyroid Deficiency of 25 per Cent; Single Graft.—Nine dogs were used. The graft could not be found in three, and the specimen was lost in one. Of the five grafts studied microscopically, all were living, three showing slight fibrosis and two marked fibrosis (fig. 1). The functional test was performed in three of these dogs by removing the remaining three glands at a second operation. Two of the dogs showed no tetany, indicating that the graft was functioning, and the third dog died of tetany. The specimen in this animal was lost.

Parathyroid Deficiency of 50 per Cent; Single Graft.—Eight dogs were used. The graft could not be found in two. Of the six grafts studied microscopically, five were living, with moderate fibrosis (fig. 2), and one was necrotic, apparently resulting from a low grade infection.

Parathyroid Deficiency of 50 per Cent; Two Grafts Placed.—One dog was used, a gland being implanted into the muscle on either side of the neck and examined microscopically two months later. Both grafts showed slight fibrosis and, as far as could be judged histologically, were functionally active (fig. 3).

Parathyroid Deficiency of 100 per Cent; Single Graft.—Twelve dogs were used. The graft could not be found in two. Of the ten grafts studied microscopically, four showed slight fibrosis, four moderate fibrosis and two were necrotic (fig. 4).

One dog was given 1 cc. of parathyroid extract subcutaneously daily for one month following operation. At the end of this period the graft was in good condition with virtually no fibrosis.

One dog was given 40 drops of viosterol daily for two months postoperatively, as well as the usual preoperative preparation. At the end of this period the graft was in good condition, with very little fibrosis (fig. 5).

Parathyroid Deficiency of 100 per Cent; Two Grafts.—Two dogs were used. All four grafts were recovered. In one dog they were living but showed moderate fibrosis at the end of one month. In the other dog both grafts were in excellent condition, with very little fibrosis, at the end of two months (fig. 6).

COMMENT

In the foregoing studies it is seen that the graft survived and in many instances retained its original size and structure in experiments in which a deficiency of only 25 and 50 per cent had been created as well as in those in which there was a deficiency of 100 per cent.[5] Most

5. In determining the degree of parathyroid deficiency a possible source of error lies in the occasional occurrence of accessory parathyroid glands. These are said (Shapiro and Jaffe: Endocrinology **7**:720, 1923) to occur in dogs with a frequency of about 6 per cent. Thus the exact degree of parathyroid deficiency in the individual experiments cannot be determined. However, this factor must have been largely canceled by the number of dogs used in each of the foregoing series of experiments. Moreover, one can assume that functionally this accessory parathyroid tissue is of little physiologic importance during the first few days after operation or during the period in which the immediate survival of the transplant is at stake, because it is never sufficient to prevent fatal tetany in dogs deprived of all four parathyroid glands unless artificial substitution therapy is given.

of the grafts showed partial replacement by fibrous tissue, and in a few of the experiments the graft could not be found. In these the graft may have been overlooked in sectioning the block of muscle or had perhaps been completely absorbed. These changes, however, were seen in the experiments in which the deficiency was 100 per cent about as frequently as in those in which it was only 25 per cent.

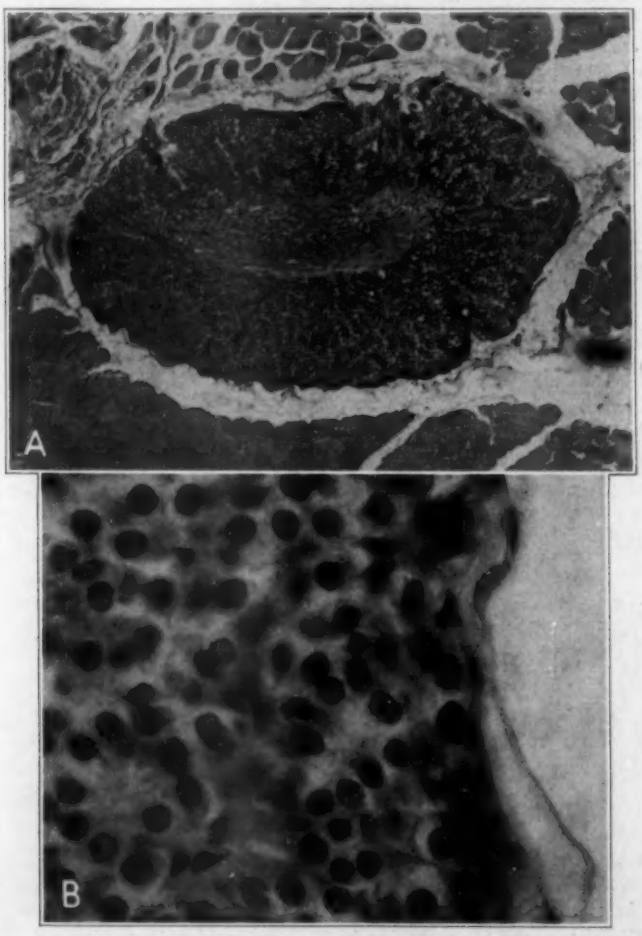

Figure 6, *A* and *B*.

Fig. 6.—Sections of muscle containing grafts removed from dog C-103, with parathyroid deficiency of 100 per cent. Two grafts were placed simultaneously, one in either side of the neck. *A* shows the graft removed from the right side after sixty days; *B*, the same section under high power magnification. *C* shows the graft removed from the left side after sixty days; *D*, the same section under high power magnification.

The microscopic study of the grafts is interesting as regards the nature of the fibrotic changes. The fibrosis was never diffuse but was

confined to the center and periphery of the transplants. This finding in itself might suggest that there was no general inhibitory endocrine factor involved. It seems likely that the central fibrosis, which was as a rule more extensive in the larger grafts, represents the initial necrosis

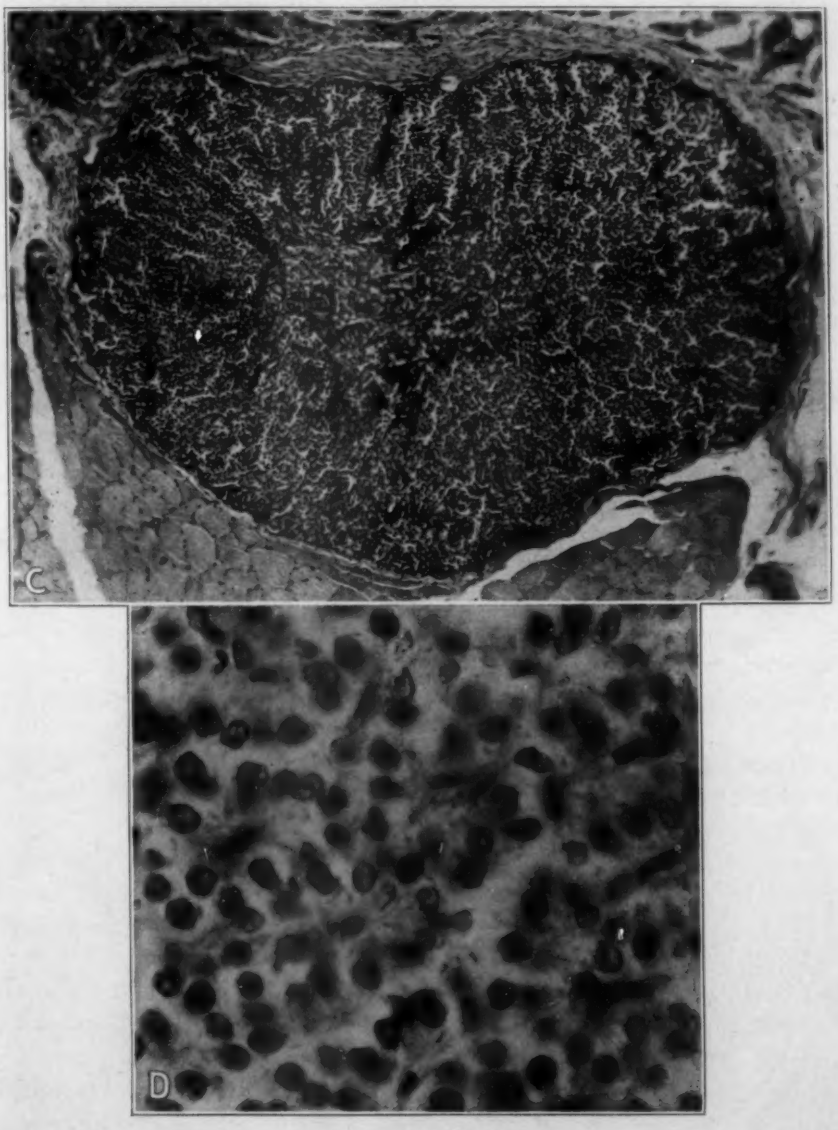

Figure 6, *C* and *D*.

of that portion which was not revascularized sufficiently soon from the surrounding muscle. The peripheral fibrosis probably represents reaction to the trauma at the time of grafting. It did not appear to be progressive as it was not more marked in grafts of two or three months' duration than in those removed for study after only two or three weeks.

This study has not included the question of the survival of the grafts over a period of years. It is possible that the factor of deficiency may play a rôle in the ultimate survival of these grafts, although my experiments have shown nothing to indicate this.

CONCLUSIONS

1. Autotransplantation of the parathyroid gland in dogs is successful when only one parathyroid gland has been removed as well as when all four have been removed.

2. When two autografts are transplanted simultaneously they may both survive when the parathyroid deficiency at the time of grafting is only 50 per cent as well as when it is 100 per cent.

3. The administration of large amounts of parathormone or viosterol does not inhibit the survival of an autograft of parathyroid tissue.

4. The urgent physiologic need of the organism for parathyroid tissue does not appear to be a requisite for the survival of the autograft.

The photomicrographs were supplied by Dr. Robert Gross.

EVISCERATION FOLLOWING ABDOMINAL OPERATIONS

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AND
GEMMA M. LICHTENSTEIN, M.D.
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The occurrence of evisceration following laparotomy seems to be unpredictable. The uncertainty of this infrequent complication is its chief terror. We have made a survey of the cases occurring in Michael Reese Hospital during the past ten years and have analyzed those factors which seemed of importance to us, without, however, being able to reach any definite conclusions.

In going through the more recent literature on this subject, we found that Sokolov [1] had analyzed the largest series. He studied reports of 732 cases collected from clinics throughout Europe and even from America. Not all the case histories gave all the information he desired. He found that almost twice as many men were eviscerated as women and that the highest incidence (55.5 per cent) was in the first six months of the year, which he thought was due to a lowering of the vitamin C content of the body. He found that incisions in the upper part of the abdomen ruptured more frequently than did incisions in the lower part, that the greatest number of ruptures were in cases of malignant disease and that operations on the stomach headed the list of types of operations after which evisceration occurred. He stated that evisceration occurs after from 2 to 3 per cent of all laparotomies. He found that the maximum number of eviscerations occurred between the seventh and the tenth day postoperatively and that the largest number occurred in patients between the ages of 30 and 60. The mortality was 32.1 per cent in cases in which resuturing was done and 35.5 per cent in cases in which it was not done.

Meleney and Howes [2] in their study found that only from 1 to 2 per cent of the abdominal operations performed at the Presbyterian Hospital in New York were followed by evisceration. They agreed with Sokolov as to the postoperative period in which most ruptures occurred. Meleney and Howes found evisceration most common after vertical

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From the Gallbladder Group, Michael Reese Hospital.

1. Sokolov, S. S.: Vestnik chir. **45-46**:219, 1931; Internat. Abstr. Surg. **55**:157, 1931; Ergebn. d. Chir. u. Orthop. **25**:306, 1932.

2. Meleney, F. L., and Howes, E. L.: Disruption of Abdominal Wounds with Protrusion of Viscera, Ann. Surg. **99**:5 (Jan.) 1934.

incisions in the upper part of the abdomen and especially frequent after operations on the gallbladder and gastro-enterostomies, and they expressed the belief that the major causes are cough, infection and gastric lavage. Their mortality rate was 44 per cent of all eviscerations.

Colp [3] expressed the belief that the underlying lesion is the important factor in evisceration.

Grace,[4] like Sokolov and Meleney and Howes, found the largest number of eviscerations after operations in the upper part of the abdomen. He found the mortality lower in those patients in whom evisceration occurred before the fifth day postoperatively than in those in whom it occurred later. White [5] agreed as to the frequency of evisceration following operations in the upper part of the abdomen.

Baldwin [6] noted that he had observed no evisceration since he began leaving sutures in place for fourteen days and keeping patients in the hospital for three weeks.

Von Gusnar [7] reported 10 cases, all in men, and listed the occurrence as 0.41 per cent of the laparotomies performed at his hospital.

Sigalas [8] published an excellent review of the literature and analyzed the 163 cases reported there plus 8 cases from his practice and that of his colleagues. He found that 127 of the patients were women, 30 were men and the sex of the remaining 14 had not been noted. He found, contrary to reports of the writers previously mentioned, that a larger number of cases were in patients with incisions in the lower part of the abdomen and that gynecological operations were the most common type. Freeman [9] also found that eviscerations occurred most commonly after operations on the lower part of the abdomen. Only 11 cases of carcinoma were listed by Sigalas. He expressed the belief that neither the type of suture nor the time of its removal is of any importance.

Starr and Nason [10] reported the results of a fifteen year survey, with 2,455 abdominal operations performed and 15 eviscerations, an incidence of 0.61 per cent. They agreed with Sigalas that eventration was most frequent after incisions in the lower part of the abdomen.

Some of the authors did not mention the number of cases on which their conclusions were based; others said nothing as to whether cases of gynecological and obstetric conditions were included in their study.

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3. Colp, Ralph: Ann. Surg. **99**:14 (Jan.) 1934.
4. Grace, R. V.: Ann. Surg. **99**:28 (Jan.) 1934.
5. White, W. C.: Ann. Surg. **99**:34 (Jan.) 1934.
6. Baldwin, J. F.: Am. J. Surg. **25**:7 (July) 1934.
7. von Gusnar, Kurt: Arch. f. klin. Chir. **150**:636, 1928.
8. Sigalas, M.: Rev. de chir., Paris **51**:32 (Jan.) 1932.
9. Freeman, L.: Causes of Postoperative Rupture of Abdominal Incisions, Arch. Surg. **14**:600 (Feb.) 1927.
10. Starr, A., and Nason, L. H.: Postoperative Rupture of Abdominal Wounds, J. A. M. A. **100**:310 (Feb. 4) 1933.

In our own investigation, we have included all cases of rupture of abdominal wounds with protrusion of the omentum or the viscera. We found 32 cases of evisceration occurring between Jan. 1, 1925, and Jan. 1, 1935. During this same period there were 12,445 abdominal operations, including 5,262 appendectomies. Most of these appendectomies were made with the McBurney incision, one which many authors feel is not conducive to evisceration. We think that it would, perhaps, make our percentage of incidence of evisceration more accurate if we subtracted most of the 5,000 appendectomies from our total number of laparotomies, leaving approximately 7,500 operations exclusive of McBurney incisions. Even with this reduction in the number of operations, our incidence of eviscerations is only 0.43 per cent, which is about the figure given by von Gusnar and is more than McCauliff's [11] but is less than any of the others.

Of the 32 patients, 10 (31.3 per cent) were men and 22 were women. Our findings in this respect agree with those of Sigalas and are the reverse of those of almost every other investigator. Sigalas and Sokolov definitely listed instances of gynecological conditions among their cases, which naturally affected the findings. Unfortunately some of the other authors failed to mention whether they included such cases or not. In our hospital there are approximately twice as many women as men having laparotomies; so this neutralizes the predominance of evisceration in women as compared with men.

The ages of our patients varied from 6 weeks to 65 years, with 70 per cent of them between the ages of 40 and 60.

As to the types of operations after which evisceration occurred, we found in our series that 13 (40.6 per cent) followed hysterectomies, of which 1 was for carcinoma and 1 for sarcoma; 6 cholecystectomies, and 4, operations on the stomach, 2 of which were resections for carcinoma and 2 were for the purpose of suturing ruptured peptic ulcers. In our whole series there were 6 cases of malignant disease, 5 of carcinoma and 1 of sarcoma; these constitute less than 19 per cent of our cases. Three eviscerations occurred after cesarean sections. Four occurred in patients operated on for intestinal obstruction.

Just as Sigalas and Starr and Nason noted more instances of incision in the lower part of the abdomen than in the upper part in their group of cases of evisceration, so we noted that 18 (56.3 per cent) of our patients had incisions in the lower part of the abdomen. We found that the median incision is most conducive to evisceration, as 20 of our patients had midline incisions. Of course one wonders what percentage of our total number of operations were made with a midline incision, but, unfortunately, such figures could be obtained only with more labor

11. McCauliff, G. T.: J. Iowa M. Soc. **23**:347 (July) 1933.

Essential Details of 32 Cases of Evisceration Following Abdominal Operation

Patient, Sex, Age	Diagnosis and Operation	Incision	Suture	Postoperative Course	Time of Evisceration (in Days Postoperatively)	Result: Other Condition
1. E. A. F 43	Adenocarcinoma of right ovary; panhysterectomy	Infra-umbilical midline	.....	Normal	13	Good
2. F. A. F 26	Pregnancy; cesarean section	Infra-umbilical midline	Tension	Broncho-pneumonia	9	Good
3. S. A. F 56	Fibromyoma; hysterectomy; salpingectomy	Infra-umbilical midline	Tension	Gangrene of buttocks; had 7 high voltage roentgen treatments before operation	11	Good; arterio-sclerotic heart disease
4. A. B. M 47	Buerger's disease; ganglionectomy	Left para-median	No tension	Coughing	6	Death; thrombi of superior mesenteric vessels
5. M. B. F 49	Fibromyoma; panhysterectomy	Infra-umbilical midline	No tension	Normal	7	Good
6. E. B. F 49	Fibromyoma; hysterectomy	Infra-umbilical midline	.....	Lavage; wound infection	9	Death
7. D. C. F 53	Carcinoma of descending colon; cecostomy	Right rectus	.....	Lavage; pulse weak; wound infection	11	Death
8. L. D. M 52	Perforated duodenal ulcer; gastro-enterostomy	Midline upper abdominal	.....	Wound infection	13	Good
9. A. D. M 42	Intestinal obstruction; exploratory	Lower left rectus	Tension	Irrational	4	Death; rupture of ileum
10. R. E. F 24	Chronic cholecystitis; cholecystectomy and appendectomy	Upper right rectus	Tension	Vomiting	8	Good
11. E. F. F 49	Fibromyoma; panhysterectomy	Infra-umbilical midline	.....	Normal	6	Good
12. A. F. F 42	Fibromyoma; panhysterectomy	Infra-umbilical midline	Tension	Vomiting	4	Death; rheumatic heart disease
13. H. G. M 38	Perforated gastric ulcer; suture of perforation	Epigastric midline	Tension	Coughing	9	Good
14. S. G. F 53	Fibromyoma; panhysterectomy	Infra-umbilical midline	Tension	Lavage	9	Good; diabetes
15. S. I. F 65	Myofibro-sarcoma; hysterectomy	Infra-umbilical midline	No tension	Coughing	8	Good
16. B. K. F 42	Fibromyoma; hysterectomy	Infra-umbilical midline	Tension	Vomiting	6	Good
17. S. L. M 40	Gastric carcinoma; resection	Epigastric	.....	Coughing	14	Good
18. V. M. M 54	Cholecystitis with stones; cholecystectomy; appendectomy	Upper right rectus	Tension	Normal	8	Good
19. H. M. F 51	Fibromyoma; panhysterectomy	Infra-umbilical midline	Tension	Normal	5	Good
20. M. M. F 30	Cesarean section	Infra-umbilical midline	Tension	Coughing	6	Good

Essential Details of 32 Cases of Evisceration Following Abdominal Operation—Continued

Patient, Sex, Age	Diagnosis and Operation	Incision	Suture	Postoperative Course	Time of Evisceration (in Days Postoperatively)	Result; Other Condition
21. E. M. F 36	Perforation of cystic duct; cholecystectomy and choledochotomy	Right hypochondrium	.....	Normal	9	Good; 4+ Wassermann reaction
22. I. M. F 38	Cesarean section	Infraumbilical	.....	.....	..	Death
23. M. P. M 50	Carcinoma of rectum; ileostomy	Infraumbilical midline	No tension	Wound infection	12	Death; hypertension; arteriosclerosis; nephritis
24. F. R. M 50	Gastric carcinoma; gastric resection	Midline epigastric	Tension	Lavage	9	Death; bronchopneumonia
25. D. R. M 6 wks.	Congenital hypertrophied colon; cecostomy	Left rectus	.....	Lavage	6 (2×) 8 (1×)	Death
26. R. R. F 44	Fibromyoma; panhysterectomy	Infraumbilical midline	Tension	Vomiting	11	Death; gallbladder stones; rheumatic heart disease
27. B. R. F 54	Common duct stone; cholecystectomy; choledochotomy	Upper right rectus	No tension	Normal	8	Good
28. G. S. F 43	Fibromyoma; panhysterectomy	Infraumbilical midline	Tension	Lavage	7	Good
29. D. S. F 37	Chronic cholecystitis; cholecystectomy	Upper right rectus	.....	Lavage	5	Death
30. E. S. F 42	Fibromyoma; panhysterectomy	Infraumbilical midline	Tension	Normal	8	Good
31. A. R. S. M 55	Appendicitis; exploratory with appendectomy	Upper right rectus	No tension	Vomiting	4	Death; peritonitis; cardiac dilatation
32. S. W. F 63	Distended gallbladder; cholecystectomy; drain	Supraumbilical and infraumbilical midline	No tension	Almost anuric	4	Death

than seems justified by the value of the results. However, we feel convinced that the percentage of midline incisions as compared to that of right and left rectus incisions is much smaller than the 62.5 per cent of eviscerations following midline incisions.

We did not feel that the method of wound closure made a great deal of difference, for almost as many types of sutures and methods of closure are used in the Michael Reese Hospital as there are surgeons working. However, in all our cases the incision was closed in layers, and in all plain or chromic catgut or both were used for the deeper layers. The skin was closed either with silk or dermal suture or with clips. In only 21 of the cases was there any definite note as to whether tension sutures were used. In 15 of these cases tension sutures were used. We believe that they are of little or no help, for in 10 cases

evisceration occurred between two tension sutures while these sutures were still in place and intact as shown at the time of secondary closure.

Most of the investigators cited who have made any note as to the most common period postoperatively in which evisceration occurs have found that in the majority of the cases the rupture occurred between the seventh and the tenth day. Of 31 cases in which we have a record of the time of the rupture, evisceration occurred in 19, or 59.4 per cent, between the sixth and the ninth day, with 6 cases each on the eighth

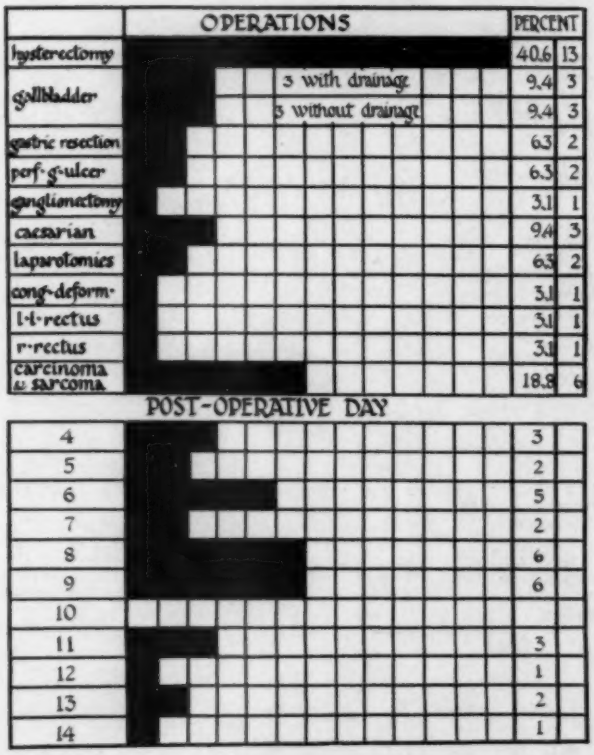

Chart 1.—Incidence of evisceration according to type of operation and number of days after the operation.

and the ninth day. Three patients had rupture of the abdominal wound as early as the fourth day and 1 as late as the fourteenth day. Of the 3 cases in which evisceration occurred on the fourth day, 1 was an instance of hysterectomy in a patient with organic heart disease and mitral insufficiency; the second was one of exploratory laparotomy for suspected cholecystitis, with an adherent, inflamed and retrocecal appendix as the only finding; the third case was one of obstruction of the transverse and descending colon by large fecal masses. Of 7 cases in which evisceration occurred between the eleventh and the fourteenth

postoperative day, 4 were instances of malignant disease. In the other 2 cases of malignant disease evisceration occurred on the eighth and ninth days. As one half of the cases in which evisceration occurred late were instances of malignant disease and as it is the tendency for surgeons to leave skin and tension sutures in longer in such cases than in the average, we wonder whether the fact that the wound was closed was not responsible for the apparent lateness of evisceration. Furthermore, it seems to us that this tends to show that the length of time that the skin sutures remain in the wound has actually very little to do with insuring the healing of the wound. This is contrary to Baldwin's belief

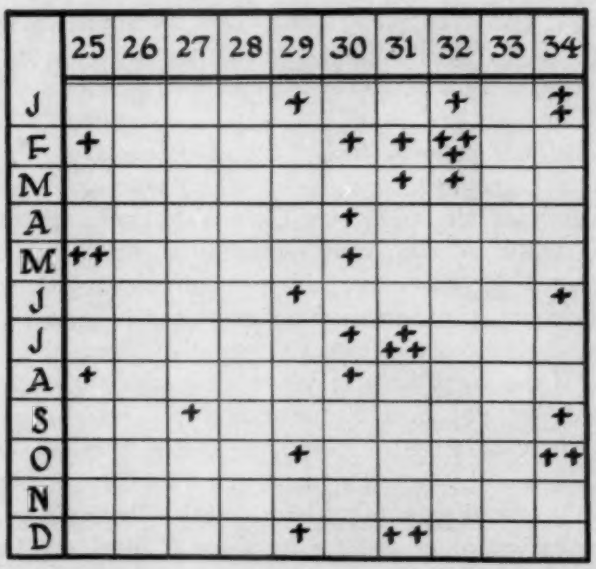

Chart 2.—Incidence of evisceration according to month and year.

that the number of his cases of evisceration has decreased owing to the longer period during which he leaves the sutures in situ.

Various authors, notably Meleney and Howes, have expressed the belief that extrinsic factors are important. They stated that cough, wound infection and gastric lavage are of great influence in causing evisceration. We found that in only 4 of the 31 cases on which we have details had wound infections occurred. This incidence is less than 13 per cent. Severe vomiting occurred in 39 per cent of our patients and severe coughing in 16 per cent. Gastric lavage was done in 7 patients, only 22.5 per cent. One patient had a positive Wassermann reaction; 2 had bronchopneumonia, of whom 1 recovered; 1 had diabetes, well controlled, and left the hospital in good condition. Two patients had rheumatic heart disease; 1 of them died suddenly

three hours after a secondary closure had been done. Two had had hypertensive heart disease and arteriosclerosis. One of these patients died. The other had a hysterectomy for fibromyoma; but previous to her admission to this hospital she had had seven high voltage roentgen ray treatments over a period of two years; while she was in the hospital and on her fourth postoperative day, a gangrenous area developed over the buttocks, which was diagnosed as a roentgen ray burn; so we cannot but question whether these treatments affected the healing powers of the patient. One patient had thrombo-angiitis obliterans with spasticity of the vessels of the leg. A ganglionectomy was done, with marked improvement in the efficiency of the circulation in the patient's legs; but evisceration occurred on the sixth day, and he died eleven days later. Postmortem examination showed arteriosclerotic stenosis and ulceration of both the mesenteric arteries and veins, with terminal thrombosis.

Twelve of our patients died. This mortality, 37.5 per cent, is in agreement with the figures given by other writers. All our patients had secondary closures. In view of Grace's statement that the mortality is lower in those cases in which evisceration occurs before the fifth day, we studied our cases from this point of view. Of the 5 patients in whom evisceration occurred on or before the fifth day, 4, or 80 per cent, died; all 3 of those in whom evisceration occurred on the fourth day died. Of the 26 patients in whom evisceration occurred after the fifth postoperative day, 8, or 31 per cent, died.

In the study of these 32 cases, the one feature which struck us most forcibly was the fact that the incidence of evisceration was not spread evenly over the ten years but seemed to occur in groups; (this fact was noted by Maes and his associates [12] likewise) for example, from August 1925 until January 1929, there was but a single evisceration, and again during the period from March 1932 to January 1934 there were no eviscerations. On the other hand, there were 2 eviscerations in May 1925, 3 in July 1931, 5 from January to March 1932, 3 during September and October 1934. This grouping of eviscerations is not explicable on the basis of epidemics of grip, bronchopneumonia or other infections. No change in operating room technic can be held accountable. During the period from March 1932 to January 1934, during which not a single evisceration occurred, a certain brand of catgut was used exclusively, while a different brand of catgut was used during the preceding and subsequent periods, in which 5 eviscerations occurred in three months and 2 in one month. However, as there have been periods of several months without an evisceration even

12. Maes, U.; Boyce, F. F., and McFetridge, E. M.: Post-Operative Evisceration with Analysis of Forty-Four Cases, Ann. Surg. **100**:968 (Nov.) 1934.

when brand B catgut was used, it is obviously impossible and unfair to stigmatize this catgut. Both brands, incidentally, come from firms of the highest reputation. Furthermore, it is interesting to note that in both instances the use of brand A was discontinued because the surgeons felt that the incidence of low grade wound infections was increased and that brand B seemed to give less trouble in this respect. In other words, the incidence of eviscerations in our series does not seem to run parallel with that of apparently poorly healing wounds.

SUMMARY

Our series of 32 cases represents all the eviscerations occurring in this hospital in the past ten years. During this time 12,445 laparotomies have been performed. Subtracting from this number most of the 5,262 appendectomies, we find that we have had 32 eviscerations after approximately 7,500 laparotomies, or an incidence of 0.43 per cent. The mortality rate after evisceration was 37.5 per cent. There were twice as many cases in women as in men, but as many more women are operated on than men, the sex of the patient apparently plays no rôle. We found evisceration occurring most frequently after operations on the lower part of the abdomen, more often after hysterectomy than after any other type of operation and more often after a midline incision than after other kinds of incision. There were 6 cases of malignant disease in the group. The eventration occurred most frequently between the sixth and the ninth day postoperatively. We do not feel that the method of wound closure or the length of time that the sutures are in place is of any great significance. Tension sutures apparently play little or no part in preventing evisceration. Complications, such as coughing, vomiting, wound infection and frequent gastric lavage, seem to be of relatively little importance. Lastly, the sporadic occurrence of our cases of evisceration and their definite grouping at certain irregular intervals, are striking.

A REVIEW OF UROLOGIC SURGERY

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(*Continued from page 576*)

URETHRA

Valves.—Counseller and Menville [49] stated that congenital valves of the posterior portion of the urethra obstruct the flow of urine and by backward pressure produce renal damage which seriously endangers the life of the patient. Anatomically, the valves may be represented by ridges, mucosal folds or fibrous diaphragms covered by mucosa, and the varieties fall into one or more of three types. In type 1, a ridge which divides into two forklike processes is continuous with the verumontanum anteriorly on the floor of the urethra. These processes are thin membranous sheets which extend upward and forward and which may be attached to the urethra through its circumference. In this group is included the nonbifurcated or single type of valve. In type 2 the ridge extends from the verumontanum toward the bladder and divides, similarly to those in type 1, that is, distal to the internal sphincter. Type 3 was first described by Jarjavy, who termed it "iris valve" because of its similarity to the shape of the iris of the eye. The iris valve occurs at various levels and is attached to the circumference of the posterior portion of the urethra. There is usually one opening in the valve, and it varies in size and in position. These three types

† Deceased.

49. Counseller, V. S., and Menville, J. G.: Congenital Valves of the Posterior Urethra, J. Urol. **34**:268 (Sept.) 1935.

serve as a general classification, but in each there are wide variations. The anomalous valves will become evident at an early age because of their obstructive symptoms. A review of 84 cases in the literature revealed that in 75 per cent symptoms appeared at or before 10 years of age and that in 52 per cent they were evident at or before the age of 5 years.

A valve which obstructs will inevitably produce hypertrophy and dilatation of the vesical wall, dilatation of the ureters and pelves and atrophy of the renal parenchyma. A funnel-shaped or relaxed vesical outlet and dilatation of the posterior portion of the urethra proximal to the obstruction are other frequent findings. In mature patients and in some young patients valvular obstruction presents a picture on cystoscopic examination which, with the exception of the vesical neck, is similar to that of prostatic obstruction which has been present for some time.

Symptoms may be classed as early and late; the early ones are produced by local obstruction and infection, while the late ones are manifestations of impaired renal function, which is secondary to urinary obstruction. In cases in which the condition affects children, fretfulness, loss of weight or failure to gain weight, a protuberant abdomen secondary to a distended bladder and difficulty in starting the urinary stream and in voiding are among the early manifestations, all of which may date back to birth.

Logical interpretation of an accurately taken history and physical examination will lead to proper urologic procedures and usually to a correct diagnosis. In cases of severe urinary obstruction, catheterization of an overdistended bladder is the first procedure; obstruction in the posterior portion of the urethra is the most usual finding.

Treatment is based on the relief of urinary obstruction. If the general condition of the patient is poor, extensive treatment should be postponed and palliative measures should be instituted. In cases in which instruments can be passed into the urethra, the condition should be treated transurethrally in a manner similar to the methods used in resection of the prostate gland.

Landes and Rall [50] stated that the etiology of valvular obstruction of the posterior portion of the urethra is not definitely established. The early anatomists regarded it as being due to dilated lacunae, aberrant folds of mucosa, adherent masses of fibrin which had become organized or inflammatory changes in the mucosa of the canal. The frequent occurrence of such obstruction in infancy and in childhood suggests a congenital origin.

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50. Landes, H. E., and Rall, Richard: Congenital Valvular Obstruction of the Posterior Urethra, J. Urol. **34**:254 (Sept.) 1935.

The symptoms of congenital valvular obstruction in the posterior portion of the urethra vary with the degree of obstruction and the presence of infection. In mild cases in which a unilateral valve is present, or when the arrangement of the valves is such as to produce a mild obstruction, there may be no symptoms until infection supervenes. In the majority of cases of urinary difficulty, a small stream, dribbling, frequency and enuresis are common symptoms. Frequency, even in the absence of infection, is common in all but the late stages of the disease because of the reduced elasticity and working capacity of the hypertrophic bladder. When infection is present there are dysuria and urgency. The intensity of the reaction depends on the type of the infecting organism and on the extent of involvement. Bacterial invasion rapidly destroys the renal tissue which has escaped hydronephrotic atrophy, and renal function is proportionately reduced.

The diagnosis frequently can be made from the history. The disease occurs in young male children in whom other types of obstruction below the bladder are uncommon. An intractable pyuria in young boys is suggestive of valvular obstruction. In advanced stages the abdomen may be prominent as a result of a dilated bladder, hydro-ureters and hydronephrotic kidneys. There is often residual urine. Cystograms usually demonstrate the presence of a dilated posterior portion of the urethra, and not infrequently remarkable ureterograms and pyelograms are obtained by reflux filling of these dilated structures from the bladder. The differential diagnosis in children includes a consideration of congenital diverticulum of the urethra, congenital stricture of the urethra, congenital hypertrophy of the verumontanum, vesical calculus and contracture of the vesical orifice.

The treatment of congenital valvular obstruction of the posterior portion of the urethra consists of surgical removal of the valves. Transurethral removal by means of Young's punch is an effective and simple method. Fulguration through the operating cystoscope and removal by small cystoscopic scissors have been successful in a number of cases. The prognosis depends directly on the amount of permanent renal damage. Renal impairment is the result of increased pressure in the urinary tract, with resulting dilatation of the ureters and renal pelvis, and is proportional to the degree and duration of the obstruction in the posterior portion of the urethra.

Reconstruction.—Harris [51] reported 5 cases in which there was complete destruction of the urethra in association with vesicovaginal fistula. Since under the circumstances for which the operation is to be undertaken the sphincter of the bladder and posterior wall of the urethra

51. Harris, S. H.: Reconstruction of the Female Urethra, Surg., Gynec. & Obst. **61**:366 (Sept.) 1935.

have been more or less completely destroyed, it is necessary not only to fashion a new urethra but also to provide it with an efficient cut-off muscle. Some tags or bands of tissue are likely to be present in the region of the urethra, especially in postobstetric cases. These should be trimmed off level with the mucosa of the vagina and allowed to heal before the plastic operation is undertaken.

The operation consisted of making a U-shaped incision surrounding the vesicovaginal orifice, the open end of the U terminating at the original site of the external orifice of the urethra. The incision was deepened for about 3 mm., and the wall of the vagina beyond the line of the incision was undermined all around to form lateral flaps. The portion of the vagina embraced by the U-shaped incision was not further disturbed, except by the sutures employed to bring its edges together in the midline to reform the urethral tube. A new sphincter was then fashioned from the muscles of the base of the bladder, and the lateral flaps were sewed together over all, the restoration of the urethra being thus completed. Actually the region of the fistula was covered by three or four superimposed layers, whereas in the lower part of the new urethra only two layers were formed. Suprapubic cystotomy concluded the operation. Urethral drainage was not used. The operation is simple and makes use of principles well known in the plastic surgical operations on the male urethra. The absence of tension leaves little room for failure when reasonable precautions are taken.

Tumors.—Scheibel [52] reported a case of primary carcinoma of the urethra in a man 71 years old. The growth occurred in the fossa navicularis, and there was metastasis to both inguinal regions. Histologically, the tumor was of squamous cell origin. Its situation was quite unusual, and as Scheibel did not believe that surgical removal would be successful, the growth was treated with roentgen rays. This treatment caused the tumor to disappear and the involved region to heal completely.

Menville [53] reviewed 10 cases of a primary malignant growth in the female urethra, bringing the total reported to 149. The majority of early lesions are located near the meatus, and it is suggested that the paraurethral duct emptying on either side of the external urethral orifice, which is susceptible to infection and trauma, is frequently the point of origin. The average age incidence is 53.4 years.

Carcinoma of the urethra grows slowly; yet the physician usually sees the patient late in the disease because of the relatively late onset

52. Scheibel, Pál: Primärer Harnröhrenkrebs beim Mann! LXII. Wissenschaftliche Sitzung der Ungarischen Urologischen Gesellschaft anlässlich der Ungarischen Arztewoche, Ztschr. f. urol. Chir. **40**:209, 1934.

53. Menville, J. G.: Primary Neoplasms of the Female Urethra, Surg., Gynec. & Obst. **61**:229 (Aug.) 1935.

of symptoms. The extent of the lesion as compared with the recent development of signs and symptoms is of some diagnostic significance. The symptoms and signs are urinary obstruction, visible tumor and chronic irritation either from infection or from trauma. The majority of the tumors are nonpedunculated, although there is no characteristic appearance in the early stage. Because the symptoms develop late in the disease, microscopic examination should be made of all tumefactions and of all caruncles, ectropions or innocent-looking papillary growths. Late in the disease the outstanding characteristics of carcinoma are induration, ulceration and bleeding and tenderness on palpation. Primary metastasis takes place in the inguinal and pelvic lymph nodes.

The results of treatment by any method are on the whole unsatisfactory. From a review of the reported cases and results in his own, Menville recommended radical extirpation of growths which are not too extensive and complete removal of which is possible. The cases best suited for surgical treatment are those in which the tumor is limited to the anterior portion of the urethra. The inguinal lymph nodes should also be removed surgically. When the growths are extensive and beyond the possibility of complete extirpation, they are probably best treated by small and repeated doses of radium and roentgen rays.

GENITAL TUBERCULOSIS

Young [54] presented a series of statistics which are in complete agreement as to the following facts concerning genital tuberculosis: The disease arises more commonly in the prostate gland and vesicles than in the epididymis. Genital tuberculosis is ultimately accompanied by tuberculosis of the lungs or kidneys in a large percentage of cases. If the seminal vesicles are involved, adequate drainage is not furnished by the ejaculatory ducts, and from this region the disease progresses downward to the epididymis or upward to the kidneys or lungs. The presence of renal tuberculosis, which has occurred in about 30 per cent of the cases, is no bar to performing the radical operation in addition to nephrectomy, and curative results may thus be obtained. The presence of old or recent tuberculosis of the lungs is often no contraindication to the radical operation; if possible, arrest of pulmonary tuberculosis should be assisted by removing the external foci of tuberculosis. If the disease is apparently localized within the scrotum, careful examinations should be made to determine that there is no involvement of the vesicles and prostrate gland before relying entirely on epididymectomy, which generally will not arrest tuberculosis of the vesicles. Radical removal of the seminal tract, epididymes, vasa deferentia, vesicles and lateral lobes

54. Young, H. H.: Tuberculosis of the Genital Tract, J. A. M. A. **104**:722 (March 2) 1935.

of the prostate gland is the operation of choice in the treatment of genital tuberculosis.

Braasch,[55] in discussing genital tuberculosis, stated that the operation for this lesion which is described by Young, and when performed by him, is a procedure that is worthy of serious consideration. Whether the average urologic or general surgeon can do as well is open to question. This is evidenced by the fact that although not many such operations have been performed, Braasch has observed 3 patients operated on elsewhere who came because of a permanent urethrorectal fistula. Care must be taken also in advising an operation that even in the most skilful hands has an immediate and late mortality as high as is shown by Young's figures. In the first place it must be decided whether so radical an operation for pangenital tuberculosis is necessary. It is well known that evidence of some form of genital tuberculosis is present in the majority of cases of renal tuberculosis. Among 1,200 patients operated on for renal tuberculosis at the Mayo Clinic, evidence of involvement of the genitalia was discovered on clinical examination in approximately 80 per cent of the cases. Surgical treatment has usually been found advisable only in the epididymis or in the testis. The tuberculous epididymis or testis should be operated on mainly because of the common tendency to suppuration and the formation of abscess. In contrast, suppuration of the prostate gland or seminal vesicles is rarely observed. The late mortality following nephrectomy for renal tuberculosis in cases of evident involvement of the prostate gland and seminal vesicles is no higher than in those without such involvement. Tuberculosis of the epididymis is arrested by heliotherapy in many cases, as has been shown by a number of observers. The difficulty in advising patients to use heliotherapy is that of securing adequate irradiation. Furthermore, extension of the disease in the epididymis with involvement of the testis is sometimes observed in spite of ideal irradiation. Braasch has observed that the tuberculous epididymis is best removed surgically before suppuration takes place and that heliotherapy should be employed as an adjunct. In this way suppuration and involvement of the testis can be obviated. Reexamination in cases in which tuberculosis of the prostate gland and seminal vesicles was found five or ten years later shows that nature has taken care of these tissues. Rectal examination usually reveals small evidence of previous infection. In some instances cicatricial areas may be felt; in others, the prostate gland and vesicles seem to have atrophied. In only an occasional case is there any evidence of an active tuberculous process. The burden of proof still rests with Young in showing that the late mortality following complete removal of the genitalia is any better than when they are left alone.

55. Braasch, W. F., in discussion on Young.[54]

[COMPILERS' NOTE.—Arguments for and against radical operations for tuberculosis of the genital tract have passed back and forth for eighteen years. After following Quinby's results and after performing a number of radical operations for this lesion, O'Conor performs simple epididymectomy, plus hygienic treatment, heliotherapy and tuberculin. At present he employs epididymectomy only in those cases in which continual suppuration causes repeated fistulas or in which heliotherapy and tuberculin do not control the lesions. After having several patients die rapidly of tuberculosis when epididymectomy was done in acutely active cases, O'Conor now insists on several months of administration of old tuberculin plus hygienic treatment before performing epididymectomy.]

Faragó [56] reported a case of primary isolated tuberculosis of the seminal vesicles. The patient complained of bloody semen. On examination the right seminal vesicle was swollen and was sensitive to pressure. Many clumps of tubercle bacilli were found in the seminal fluid. Tuberculosis was not found in the rest of the urogenital system or elsewhere in the bladder. The patient was under observation for three and a quarter years, and the condition remained isolated.

HEMATURIA IN PREGNANCY

Morris [57] reported that in a routine study of 154 cases of disturbance of the urinary tract during pregnancy, hematuria occurred in 30 cases. Cystitis was present in all of these cases. Pyelitis occurred in 22 cases, in 20 being bilateral and in 2 unilateral. Hydronephrosis occurred in 10 cases, in 2 being bilateral and in 8 unilateral. Pyonephrosis of the right kidney occurred in 2 cases. There was ptosis of the kidney in 9 cases; it was bilateral in 4 cases, on the right side in 4 and on the left in 1. Megalo-ureter was observed in 11 cases; in 4 it was bilateral, in 6 on the right side and in 1 on the left side. There was calculus of the right ureter in 2 cases, and ureteritis was present in 2 cases, in 1 bilaterally and in the other on the right side. Morris concluded that hematuria is a grave complication of pregnancy and that the patient should have a thorough urologic investigation.

URINARY INFECTION

Crance and Maloney [58] presented a new treatment for bacilluria of the Escherichia variety, in which nitrohydrochloric acid is used. This acid

56. Faragó, György: Fall einer primären, isolierten Samenblasentuberkulose: LXI. Wissenschaftliche Sitzung der Ungarischen Urologischen Gesellschaft, Ztschr. f. urol. Chir. **40**:207, 1934.

57. Morris, H. L.: Hematuria as a Complication of Pregnancy, J. A. M. A. **105**:403 (Aug. 10) 1935.

58. Crance, A. M., and Maloney, T. W.: A New Acid Medication in the Treatment of Bacilluria, J. Urol. **33**:657 (June) 1935.

reduces the p_H to 5 or below in apparently less time than the ketogenic diet and can be administered to the patient without the need of hospitalization and without change in the ordinary diet. So far, urinalysis, regularly done in all cases, has failed to show any renal damage by consistent absence of albumin and casts. In 1 of the cases reported in which the ketogenic diet failed utterly, the patient recovered completely under treatment with nitrohydrochloric acid. Crance and Maloney stated that it has been their custom to continue this treatment for approximately one week after culture of the urine has become sterile.

Braasch [59] stated that the usual methods employed in combating persistent urinary infections, including medication with so-called urinary antiseptics, the administration of vaccines and serums and the use of bacteriophage, are in most cases unsatisfactory. The discovery by Helmholz and Clark of a method of inhibiting bacterial growth in the urine by means of ketosis and acidification has given an accurate and scientific method of treatment. The therapeutic value of ketosis in the treatment of bacillary infections of the urinary tract has been established by experience with several hundred patients in the past three years at the Mayo Clinic. Although the establishment of ketosis is the major portion of the treatment in many cases of infection of the urinary tract, it is often inefficient unless aided by other therapeutic measures. In the majority of cases the critics of the ketogenic diet, who have failed to obtain satisfactory results, have overlooked the following factors: meticulous administration of the diet, complete elimination of persistent foci of infection and attention to the presence of a mixed infection, which requires methods of treatment other than the ketogenic diet. Even in its present simplified form it is questionable whether treatment with the ketogenic diet should be attempted unless the diet is controlled by some one familiar with dietary regimens and the patient is kept under daily observation. One of the most significant obstacles to successful treatment of bacilluria is caused by reinfection from a persistent prostatitis. Frequently usual methods of treatment, consisting of prostatic massage, dilation of the urethra and deep instillations, are unsatisfactory in eliminating this focus of reinfection. In accordance with the suggestions of Grant, attempts have recently been made at the Mayo Clinic to control prostatic infection by intraprostatic injections of mercurochrome. In one case, on two occasions 10 cc. of a solution of mercurochrome was injected into the prostate gland, and apparently this was a definite factor in diminishing the degree of prostatic infection. Although experience with this type of injection has not been sufficient

59. Braasch, W. F., in discussion on Control of a Severe Form of Chronic Pyelonephritis and Prostatic Infection by the Ketogenic Diet, Proc. Staff Meet., Mayo Clin. **10**:596 (Sept. 18) 1935.

to form any definite conclusions, a number of cases have been observed in which there has been marked improvement following its use.

PYURIA

Briggs [60] presented a review of the literature on so-called aseptic pyuria and reported 3 cases of the condition. Two of the most reasonable views in regard to the etiology are that the infection is caused by a filtrable virus or ultramicroscopic micro-organism and that the gram-positive organisms entrenched in the renal parenchyma cause an inflammatory reaction with an exudation of pus into the renal pelvis. The latter theory is substantiated by the facts that Runeberg found staphylococci in the lesions of kidneys he removed for this condition, that when any organisms were found in the laboratory they were staphylococci and that neoarsphenamine is almost a specific in the treatment of renal infections caused by gram-positive organisms and acted like a specific in these cases. Neoarsphenamine was remarkably effective in the cases of Gross, Neckers, Bumpus and the 3 cases herein reported. Briggs was of the belief that it should be more extensively used in order to prevent nephrectomy in cases of unilateral pyuria and continuous severe suffering in cases of bilateral pyuria. Since neoarsphenamine may cause exfoliative dermatitis, anemia and acute yellow atrophy of the liver, it should not be used until other less dangerous medicines have been tried.

URINARY ANTISEPSIS

Heathcote [61] has made a very thorough study of hexamine, from the standpoint, first, of its rate of hydrolysis at different hydrogen ion concentrations and, second, of its antiseptic power against various bacteria in urine. In the first part of the study the rate of hydrolysis into formaldehyde was determined with and without standard buffer solutions. All the methods in common use for the estimation of formaldehyde are either rendered invalid by the presence of hexamine or require the use of strong acids or alkalis, with or without the use of heat, both of which substances will evidently completely upset the determination of the rate of hydrolysis at a definite p_H. The method finally adopted was the determination of freed ammonia by indirect titration. Ten series of experiments were performed at different values of p_H, varying from 0.1 to 7. Each series was carried out at three ranges of temperature: (1) 37 C. (7) and 37.5 C. (3); (2) 32 C. (4), 31.5 C. (4) and 30.5 C.

60. Briggs, W. T.: Neoarsphenamine in So-Called Sterile Pyuria, J. Urol. **34**:230 (Sept.) 1935.

61. Heathcote, R. St. A.: Hexamine as an Urinary Antiseptic: I. Its Rate of Hydrolysis at Different Hydrogen Ion Concentrations; II. Its Antiseptic Power Against Various Bacteria in Urine, Brit. J. Urol. **7**:9 (March) 1935.

(2), and (3) at room temperature, varying from 29.5 to 23 C. In the first three series, at p_H 0.1, 0.4 and 0.8, respectively, no buffering substances were employed. In the remainder, standard buffer solutions were used.

Heathcote concluded that: (1) In solutions of p_H from 0.1 to 1.1, the hydrogen ion concentration is the determining factor in the rate of the hydrolysis, the velocity constant for the reaction varying directly with it; (2) in solutions not more acid than about hundredth-normal, the velocity constant is not solely dependent on the hydrogen ion concentration, being far greater than would be expected if the relation mentioned in the previous paragraph held good, and (3) this may probably be accounted for by (*a*) the presence of neutral salts in the buffered solutions, and by (*b*) hydrolysis being partially brought about by the undissociated fraction of acid salts there present.

The second part of the study dealt with the antiseptic power of hexamine against various bacteria in the urine. This depends largely on the ultimate strength of formaldehyde in the urine at any definite point. It will be determined by the percentage of hexamine present, which in turn depends on the dose administered, the proportion of that dose which is destroyed elsewhere in the body and the volume of urine secreted. With a known amount of hexamine present in the urine the amount of formaldehyde will depend on: (1) the hydrogen ion concentration of, and the amount of neutral and acid salts present in, the urine, and (2) the time factor, in that during the continuous process of the secretion of urine each molecule of hexamine is exposed to the hydrolytic process in acid urine from the moment of its excretion by the kidney until it is finally voided. A further important point is the time required by a definite concentration of formaldehyde to kill any given organism or the strength required to prevent the growth of that organism. Three strains of bacteria, Staphylococcus aureus, Bacillus coli-communis and Bacillus coli-alcaligenes, each recently isolated in a case of infection of the urinary tract, were used. Three sets of experiments with hexamine were performed, at p_H 5, 6 and 7, respectively, while a fourth was carried out at p_H 8.5, borax being used in place of hexamine. Each of these sets was duplicated by using as a medium in the one case an aqueous buffered solution and in the other urine, both brought to the desired p_H, which was checked by the use of indicators.

Heathcote found that the effect of exposure at 37 C. for periods of three and of six hours of Staph. aureus, B. coli-communis and B. coli-alcaligenes to a 1 : 500 solution of hexamine at p_H 5, 6 and 7 was as follows: (1) at p_H 7, no definite effect on the growth of any of these organisms could be observed even after six hours; (2) at p_H 6, three hours' exposure produced no effect in the case of Staph. aureus, a

doubtful effect with B. coli-communis and a considerable effect in the case of B. coli-alcaligenes; six hours' exposure produced a doubtful effect in the case of Staph. aureus, but a well marked action on the other organisms; (3) at p_H 5 the growth of Staph. aureus was definitely reduced by six, but only doubtfully by three, hours' exposure; in the case of the other organisms the acidity of the medium itself was sufficient to obscure the effect of hexamine, (4) similar experiments with borax, in a dilution of 1:500 and at p_H 8.5, showed no effect to be produced on Staph. aureus but a considerable reduction in growth in the case of the other organisms.

Two factors are of the greatest importance in the question as to whether an antiseptic strength of formaldehyde will be reached in the urine of a patient taking hexamine: time and the reaction of the urine. In cases of infection of the upper part of the urinary tract there will not be sufficient time for such a strength to be developed. In cases of acute cystitis, urine sufficiently acid to produce such a strength of formaldehyde will cause such pain and frequency of micturition as to prevent any effective action. In cases of chronic cystitis there may be hope of reaching an antiseptic strength of formaldehyde over a period long enough to be effective. Hexamine might be a valuable prophylactic in cases in which repeated catheterization is needed. Borax might be of value in the treatment of acute or chronic cystitis, especially if due to a coliform organism.

UROGRAPHY

Cahill [62] stated that tumors and enlargements of the adrenal glands have been diagnosed by roentgen examination, either through the density of the shadow made by the tumor itself or through displacement by the tumor of some shadow-forming organ, such as the kidney.

Langeron in 1929 showed that intraperitoneal injection of air would permit visualization of an adrenal tumor. Since 1930 Cahill has used injections of gas after the manner of Carelli for the determination of pathologic conditions in the renal region. This has been of value in cases of tumor adjacent to the kidney, particularly for tumors of adrenal origin. At first the method used was that described by Carelli, with the introduction of a measured amount of gas by transferring fluid from one cylinder to another, driving the measured amount into the perirenal space under a definite known pressure of gravity. This was modified by using air instead of carbon dioxide, and the procedure was simplified by using a manometer in the manner of introducing air into the pleural cavity. The method was further simplified by straight

62. Cahill, G. F.: Air Injections to Demonstrate the Adrenals, J. Urol. **34**: 238 (Sept.) 1935.

injection of the measured amount of air directly into the perirenal space by hand pressure, with no attempts to measure the amount of pressure. It was then ascertained that the injected air could be displaced in the desired direction by manual pressure and that the air would more or less slowly infiltrate through the fascial planes, so that roentgenograms taken twelve, eighteen, twenty-four or thirty-six hours later would show the organs and fascial planes clearly, especially around the adrenal gland. This method has been found to be of value in demonstrating both pathologic and normal adrenal glands. Tumors of the adrenal gland, such as adenoma and carcinoma, as well as hypertrophied bilateral adrenal glands, have been shown. Of special value is the determination of a normal adrenal shadow on the opposite side when an adrenal tumor is present.

No ill effects have resulted from the procedure. There are no particularly large vessels in the area of injection. Whether the trochar is in a blood vessel may be easily determined by aspiration. The introduction of air produces a slightly uncomfortable feeling of pressure, which rapidly disappears. The air at times works down into the psoas fascia and has produced some crepitation in the thigh over Scarpa's triangle, but this usually disappears in a few days.

With the patient on his side, the area of the flank is sterilized. Procaine hydrochloride is injected into the site of the injection as well as into the tract. The trochar is then introduced, usually below the twelfth rib, in an area between the outer border of the erector spinae muscle and the reflection of the peritoneum. As the trochar passes through the transversalis fascia the change in resistance is noted; it is then passed a short distance upward and inward. At this point changes in manometer readings on inspiration and expiration show whether the open end of the trochar is in the renal fascia. Attached to the trochar is a sterile glass tube filled with sterile cotton which acts as an air filter. This is further connected to a rubber bag and then to a measure pump. Between 200 and 250 cc. of air, depending on the size of the patient, is introduced into the bag and is then slowly forced by hand from the bag through the cotton and trochar into the perirenal fascia. A film is then taken and developed. This shows where the air is located. It then may be displaced upward or downward in the fascial planes by manual pressure. The films that have most satisfactorily shown the fascial planes have been those taken eighteen or twenty-four hours later. In these the air has been well diffused.

Wesson [63] stated that intravenous urography has restored a large portion of the field of medicine to the general practitioner. It should

63. Wesson, M. B.: Intravenous Urography for the General Practitioner, South. M. J. **28**:16 (Jan.) 1935.

be recognized, however, that it is only another diagnostic procedure, and its findings should be checked as far as possible by retrograde cystoscopy. Intravenous injections of urographic mediums are found valueless in severe cases of pyelitis of infancy, as there is no excretion of the medium owing to the pyelonephritis. This test will supplement and make valuable the routine health examinations. At present the general practitioner only examines the urine chemically and occasionally palpates the kidney. In the future he will make intravenous urograms and find lesions which necessitate surgical intervention in their early stages.

Dos Santos [64] described his method of arteriography for the diagnosis of renal and adrenal tumors. Arteriography is an aid and may be the deciding factor in making a differential diagnosis, especially in obscure cases. The aortographic diagnosis is based on the course, extension and number of the renal arteries. Accurate knowledge of the normal anatomic situation is essential for the successful judging of the picture obtained. Impressive examples are offered of the differential diagnosis of hypernephroma, cancer and angioma. In hypernephroma the affected parenchyma does not contain vessels; in carcinomatous kidneys the vessel channels and the width of the arteries are irregular; partly formed new blood vessels are seen, and in some areas the eroded vessels form small lakes of blood. In 1 case, because of unusually numerous and ramifying vessels, a diagnosis of bilateral renal angioma was made, which was verified at operation. In another case, in which a clinical diagnosis of new growth had been made, arteriography showed that only an arteriosclerotic nephritis was present. The picture of the vessels in this condition is very characteristic. In cases of suprarenal tumor it is possible for a skilful technician to note the typical displacements and determine between retroperitoneal growths and hepatic or splenic enlargements. Cases of echinococcus cyst of the liver, sarcoma of the spleen and splenic cyst are discussed.

STATISTICS ON UROLOGIC SURGERY

Counseller [65] reported that at the Mayo Clinic in 1934, 1,636 operations were performed on the genito-urinary tract, consisting of 2,343 surgical procedures on 1,403 patients. There were 23 deaths, a mortality of 1.6 per cent. These figures represent an increase of 16.6 per cent in the number of patients and 34.5 per cent in the number of surgical procedures over that of the preceding year. This is accounted for

64. Dos Santos, Reynaldo: L'aortographie dans les tumeurs rénales et pararénales, Arch. d. mal. d. reins **8**:313, 1934.

65. Counseller, V. S.: A Survey of Surgical Urology for 1934, Proc. Staff Meet., Mayo Clin. **10**:515 (Aug. 14) 1935.

by the increase in the number of patients presenting themselves for transurethral resection of the prostate gland.

In cases of carcinoma of the bladder the most effective operation is total removal of that organ, provided the carcinoma is confined within its walls, with transplantation of the ureters either to the sigmoid colon or to the skin. The latter procedure is safer than the former, but the patient is disturbed considerably by the constant presence of urinals on the thighs. Grading of tumors of the bladder is sound fundamentally, and, as Keyes has stated, all epithelial tumors of the bladder graded 1 or 2 should be regarded as curable and should be treated by fulguration or implantation of radon, or by cystectomy or other operative procedures. The prognosis for lesions of grade 3 and 4 is poor after any surgical method. Highly malignant lesions, with a base measuring more than 2 cm. in diameter, are practically hopeless no matter what surgical attack is used. During 1934, 61 patients with carcinoma of the bladder were treated by 71 major surgical procedures, consisting of segmental resection, fulguration, cautery, application of radium, excision, ureterosigmoidal anastomosis, total cystectomy and ureterostomy. Every available method was utilized, and in each instance the method of attack was governed largely by the size, situation and grade of malignancy of the tumor. The most satisfactory results were obtained in cases of small lesions of a low grade of malignancy. Twenty-three patients were treated by combined excision, electrocoagulation, cautery and the application of radium; 14, by segmental resection, and 6, by segmental resection and reimplantation of the involved ureter. There were 4 deaths in the entire group. The lesions in these cases were graded 4 in 3 cases and 3 in 1 case. All of the lesions were extensive and confined to the region of the trigon and vesical neck. It is generally agreed that for small lesions of a low grade of malignancy the transurethral approach is satisfactory, but for more extensive lesions of a low grade and for all lesions of higher grades of malignancy the suprapubic approach should be used. If such lesions are confined to the mucosa or portions of the wall, the possibility of cure is good. If a case is suitable for bilateral ureterosigmoidal anastomosis and total cystectomy, complete removal of the bladder seems necessary. However, if a ureter has been damaged by obstruction and infection, the risk is too great to justify the procedure. It is safer to perform bilateral cutaneous ureterostomy and cystectomy.

In 1934 it was necessary to remove stones from the ureters by ureterolithotomy in 40 cases. Other surgical procedures on the ureter consisted of ureterotomy and ureterostomy for tuberculosis, either of the ureter or of the bladder, plastic operations on the ureter for obstruction and transplantation of the ureter into the bladder for urinary

incontinence because of anomalous ureter. Transplantation of the ureter was performed in 8 cases: in 4 of exstrophy, in 2 of interstitial cystitis, in 1 of cystitis and contracted vesical neck, and in 1 of epispadias. This operation is of value when more conservative methods are not practicable for the treatment of severe vesicovaginal fistulas, particularly those produced by application of radium to carcinoma of the cervix, and in an occasional case in which the floor of the pelvis and neck of the bladder have been damaged beyond repair by parturition. The mortality is about 5 per cent, so that the operation should not be denied any patient for whom it is definitely indicated.

Among 356 patients with conditions of the kidney treated surgically there were only 7 deaths. Frequently complicating conditions modified the standard treatment. The cases were divided into groups: nephrolithiasis with or without hydronephrosis, pyelonephritis or pyonephrosis; hydronephrosis without stones; malignant lesions of the kidney, and miscellaneous renal conditions. In the first group there were 122 cases. In 26 of these one kidney was functionless or so damaged that nephrectomy was performed. Stones, single or multiple, were removed from the renal pelves of 78 patients without fatality. Forty patients who had hydronephrosis without stones were subjected to 67 surgical procedures. In such cases conservative or restorative operations are indicated because not infrequently the lesion is bilateral and often one kidney has been removed for a similar condition. In 21 cases, approximately 50 per cent, the involved kidney had been partially obstructed so long that it was functionless and nephrectomy was carried out. If the condition involved the other kidney, either a plastic operation on the renal pelvis or permanent nephrostomy was done. Nineteen patients underwent single or multiple conservative operations for various degrees of hydronephrosis.

Twenty-eight patients with malignant lesions of the kidney underwent nephrectomy; of the lesions, 15 were hypernephromas. There were 5 children with Wilms' tumors. The other lesions were hemangioendothelioma, epithelioma and sarcoma. In 1 case there was an extensive primary carcinoma of the adrenal gland; the kidney was adherent to it, and since the lesion was of grade 4, the kidney was removed together with the tumor. In this case clinical symptoms characteristic of adrenal tumor were absent.

On the external genitalia 799 surgical procedures were performed for cryptorchidism, hypospadias, epididymitis, tumor of the testis, varicocele, hydrocele and phimosis or redundant prepuce. Fifty-nine of these procedures were done on 35 patients with cryptorchidism. The Torek and Cabot operations continue to be the procedures of choice and were performed on 27 patients. The Cabot operation is indicated

if the spermatic cord is of adequate length, if the scrotum is fairly well developed and if it is desired to maintain temporary traction while the patient is in the hospital. Good results from the Torek operation were obtained in approximately 95 per cent of cases. Orchidectomy was performed on 10 patients with malignant lesions of the testis. Some others were treated only with roentgen rays. Some received roentgen treatment prior to operation, and all received it after operation. At present quantitative estimation of excretion of a follicle-stimulating hormone in the urine is not a sufficiently accurate index of the histopathologic characteristics of a tumor. The technic of orchidectomy is such that the operation can hardly be contraindicated in any case; the primary tumor is not only removed, but the type of tumor cell present can be determined. The discovery that this hormone is excreted in the urine of men who have malignant lesions of the testes and not in that of other men has added much to the knowledge of this disease. The greater the amount of hormone excreted the higher the grade of malignancy. Furthermore, if the rate of excretion is affected little by roentgen therapy and if the rate of appearance in the urine is persistently high, the prognosis is poor.

Walters [66] stated that the early plastic operations for hydronephrosis were developed by Kuster, Trendelenburg, Bazy and Christian Fenger. Several successful operations of the Fenger type were performed at the Mayo Clinic for hydronephrosis prior to 1920. Approximately 75 plastic operations for hydronephrosis have been performed at that institution since 1927. Some of the procedures used in these cases have been resection of the hydronephrotic renal pelvis, reimplantation of an abnormally placed ureter into a hydronephrotic renal pelvis and, in 1 case, ureteropyeloneostomy. Removal of infected portions of duplicated kidneys affords a suitable field for conservative renal surgical treatment.

Another field for transplantation of the ureters to the sigmoid is in cases of contracted bladder following removal of a tuberculous kidney. Submucosal transplantation of the ureter into the sigmoid was performed in 2 such cases, in 1 for a contracted bladder caused by tuberculosis and in the other for diffuse submucosal inflammation of the bladder. Ureterosigmoidal transplantation may be used in selected cases of inoperable carcinoma of the bladder in which total cystectomy is to be performed. Its main application is in cases of exstrophy of the bladder; more than 100 patients with this type of lesion have been operated on at the Mayo Clinic.

66. Walters, Waltman: Plastic Operations on the Genito-Urinary Tract: I. Operation on the Ureters and Kidneys, Proc. Staff Meet., Mayo Clin. **10**:529 (Aug. 21) 1935.

Cabot [67] noted the different development of operations for transplantation of the ureters to the intestine in this country as compared with those in Europe. In the latter a number of the best known experts have largely abandoned the operation because of the high mortality, which is from 25 to 35 per cent. In contrast to this, there are cases such as those reported from the Mayo Clinic by Walters in which in a series of approximately 100 cases there has been a mortality of less than 5 per cent and excellent results have been obtained. It is Cabot's opinion that this difference is due to the selection of cases. Many of the European operators have used uretero-enterostomy for patients with badly damaged ureters and commonly for patients with cancer of the bladder, who are obviously unsatisfactory risks. The most favorable results from this operation can be expected only when performed on substantially normal ureters and on patients in relatively normal general condition. The transplantation of the abnormal ureter or the transplantation of the practically normal ureter of an extremely debilitated patient will not give satisfactory results. If these limitations are taken into consideration, the evidence warrants the assertion that uretero-enterostomy has achieved a permanent position, although it need not be assumed that it will generally leave the patient with entirely normal kidneys for the rest of his life.

UROLITHIASIS

Reaser [68] studied a series of approximately 5,900 reports of necropsies to ascertain the incidence of urolithiasis and to compare the prevalence of stones in the white and Negro races. Seventy-nine cases of urinary calculi were recorded, in 14 of which the patients were Negroes. Data were not available to determine the ratio of Negroes to white persons in the complete necropsy series. No stone was found in a Negro less than 50 years of age, and the majority were 60 years or older. In practically all cases in which stones were found a disease process in the kidneys either preceded or accompanied lithiasis. The conclusion is that urolithiasis is uncommon in Negroes and that when it occurs the patient is at an advanced age.

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67. Cabot, Hugh, in discussion on Walters.[66]

68. Reaser, E. F.: Racial Incidence of Urolithiasis, J. Urol. **34**:148 (Aug.) 1935.

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